CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211488Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Type 5 NDA submitted via the 505(b)(2) regulatory pathway
Application Number(s)	211488
Priority or Standard	Standard
Submit Date(s)	July 27, 2020
Received Date(s)	July 27, 2020
PDUFA Goal Date	May 27, 2021
Division/Office	Division of Oncology 1/Office of Hematology & Oncology Products
Review Completion Date	May 12, 2021
Established Name	Leuprolide mesylate
(Proposed) Trade Name	Camcevi
Pharmacologic Class	Gonadotropin releasing hormone agonist
Code name	L02A E02
Applicant	Foresee Pharmaceuticals Co., Ltd.
Formulation(s)	Injectable suspension
Dosing Regimen	50 mg Q 6 months
Applicant Proposed Indication(s)/Population(s)	The palliative treatment of advanced prostatic cancer
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with advanced prostatic cancer

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
ADT	androgen deprivation therapy
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BLA	biologics license application
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
ELISA	enzyme linked immunosorbent assay
ECOG	Eastern Cooperative Oncology Group
ENT	Ear/ Nose/ Throat
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GnRH	gonadotropin releasing hormone
HCP	Healthcare Providers
IDMC	Internal Displacement Monitoring Centre
iPSP	Initial Pediatric Study Plan
IND	Investigational New Drug
ITT	intent to treat
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD	listed drug
LH	luteinising hormone
LMIS	leuprolide mesylate injectable suspension
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
NMP	N-methyl-2-pyrrolidone
NOAEL	no observed adverse effect level
OCE	Oncology Center of Excellence
OPQ	Office of Pharmaceutical Quality

PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLA	poly (D,L-lactide)
PP	per protocol
PSA	prostate-specific antigen
PT	preferred terms
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	standard of care
TEAE	treatment emergent adverse event
TK	toxicokinetics
URRA	user risk related analysis
WRO	written response only

1 Executive Summary

1.1 Product Introduction

Leuprolide is a gonadotropin-releasing hormone (GnRH) agonist, and Camcevi is a sterile formulation of the leuprolide mesylate for subcutaneous injection. The Applicant submitted this NDA submission as a 505(b)(2) application for the same indication as the listed drug Lupron injection (leuprolide acetate; NDA 019010) and is relying on FDA's previous findings of nonclinical safety for the listed drug by providing clinical bridging data. This submission is a complete resubmission of the original NDA submission dated March 28, 2019 for which FDA issued a Refuse to File Letter on May 23, 2019.

1.2 Conclusions on the Substantial Evidence of Effectiveness

This NDA is supported by one single arm, open-label clinical trial (FP01C-13-001) in which leuprolide injectable emulsion was administered to 137 patients with advanced prostate cancer who were judged to be candidates for androgen deprivation therapy (ADT). Leuprolide injectable emulsion was administered as two subcutaneous injections of 42 mg each on Days 0 and 168. Serum testosterone levels were measured at regular intervals from Day 28 through Day 336. The extention phase (FP01C-13-001-EX) collected additional safety data on 30 patients who continued treatment after Day 336. The primary objective was to demonstrate the ability of leuprolide injectable emulsion to achieve a serum testosterone level ≤ 50 ng/dL by Day 28 and maintained through Day 336, estimated by the Kaplan-Meier method.

In the primary efficacy analysis of clinical trial FP01C-13-001, 97% (95% CI: 92.2, 98.9) of patients maintained serum testosterone levels ≤ 50 ng/mL between Day 28 and 336. This result met its primary efficacy endpoint as the lower bound of the 95% CI was 92.2%. Sensitivity analyses of the primary efficacy endpoint were generally in line with the primary analysis. With regard to secondary efficacy endpoints, leuprolide injectable emulsion suppressed serum testosterone below the more stringent threshold of 20 ng/dL in 69% of subjects by Day 28, reduced mean serum LH levels by approximately 90%, confirming that the therapeutic effect is achieved by inhibiting LH release, and reduced serum PSA levels. This trial and its efficacy analyses generally followed the recommendations outlined in the FDA Guidance for Industry on Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone (GnRH) Analogues (https://www.fda.gov/media/129027/download).

The overall pattern of AEs reported in clinical trial FP01C-13-001 is consistent with that expected in men in the demographic group and the disease under study, and are consistent with toxicities reported in published clinical trials and post-marketing reports of leuprolide. Warnings and Precautions included in Section 5 of product labeling for Camcevi include tumor

flare, hyperglycemia and diabetes, cardiovasculat disease, QT/QTc prolongation, convulsions, and embryo-fetal toxicity. The most common (>10%) adverse reactions, including laboratory abnormalities, were hot flush, decreased hemoglobin, hypertension, increased blood glucose, injection site reactions, upper respiratory tract infections, musculoskeletal pain, fatigue, and pain in extremity.

All review disciplines are in favor of regular approval of camcevi. There is one postmarketing commitment as follows:

Develop a separate, specific, complimentary method to determine the degradant at RRT (b) (4) (b) (4) *. Submit a CBE-30 supplemnt to update the drug product specifications with the new method for RRT* (b) (4) *. In the supplement, provide a description of the new method as well as the validation.*

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

This NDA is supported by one single arm, open-label clinical trial (FP01C-13-001) in which leuprolide injectable emulsion was administered to 137 patients with advanced prostate cancer who were judged to be candidates for androgen deprivation therapy (ADT). Leuprolide injectable emulsion was administered as two subcutaneous injections of 42 mg each on Days 0 and 168. Serum testosterone levels were measured at regular intervals from Day 28 through Day 336. The extention phase (FP01C-13-001-EX) collected additional safety data on 30 patients who continued treatment after Day 336. The primary objective was to demonstrate the ability of leuprolide injectable emulsion to achieve a serum testosterone level ≤ 50 ng/dL by Day 28 and to maintain that level through Day 336.

In the primary efficacy analysis, 97.0% (95% CI: 92.2, 98.9) of patients maintained serum testosterone levels ≤ 50 ng/mL between Day 28 and 336, estimated by the Kaplan-Meier method. The trial met this primary efficacy endpoint, as the lower bound of the 95% CI was 92.2%. Sensitivity analyses of the primary efficacy endpoint were generally in line with the primary analysis. With regard to secondary efficacy endpoints, leuprolide injectable emulsion suppressed serum testosterone below the more stringent threshold of 20 ng/dL in 69% of subjects by Day 28, reduced mean serum LH levels by approximately 90%, confirming that the therapeutic effect is achieved by inhibiting LH release, and reduced serum PSA levels. This trial and its efficacy analyses generally followed the recommendations outlined in the FDA Guidance for Industry on Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone (GnRH) Analogues (https://www.fda.gov/media/129027/download).

Known adverse effects of androgen deprivation include acceleration of atherosclerosis, prolongation of the QT interval, osteoporosis, hyperglycemia, anemia, cognitive decline, gynecomastia, hot flashes, and loss of libido. Many of these effects are nonspecific and common in aging individuals. The overall pattern of AEs reported in FP01C-13-001 is consistent with that expected in men in the demographic group and the disease under study, and are consistent with toxicities reported in published clinical trials and post-marketing reports of leuprolide. Warnings and Precautions included in Section 5 of product labeling for Camcevi include tumor flare, hyperglycemia and diabetes, cardiovasculat disease, QT/QTc prolongation, convulsions, and embryo-fetal toxicity.

All review disciplines are in favor of regular approval of camcevi.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The American Cancer Society estimates that there will be 248,530 new cases and 34,130 deaths from prostate cancer in the United States in 2021. The five-year survial rate is approximately 30% for patients with distant disease.[1]	Prostate cancer is a serious and life-threatening disease.
Current Treatment Options	• Reports in the 1940s of dramatic responses after bilateral orchiectomy led to the widespread adoption of this procedure in men with advanced prostate cancer.[2,3] Androgen deprivation therapy (ADT) remains the mainstay of therapy for patients with metastatic prostate cancer. All available options – estrogens, orchiectomy, and GnRH agonists, with or without an anti-androgen – produce response rates of 80 to 90% and median response duration of 18 to 24 months.[4]	ADT with GnRH agonists is a widely used first-line treatment for men with advanced prostate cancer.
Benefit	• Trial FP01C-13-001 met it primary endpoint, as 97.0% (95% CI: 92.2, 98.9) of	Single-arm clinical trials demonstrating the

[1] American Cancer Society: Cancer Facts and Figures 2021. American Cancer Society, 2021.
[2] Huggins C, Hodges CV. Studies on prostatic cancer: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293-297.
[3] Huggins C, Stevens RE, Hodges CV. Studies of prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;42:209-23.
[4] Peeling WB. Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic cancer. Urology 1989;33(5 Suppl):45-52.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients maintained serum testosterone levels ≤ 50 ng/mL between Day 28 and 336. With regard to secondary efficacy endpoints, leuprolide injectable emulsion suppressed serum testosterone below the more stringent threshold of 20 ng/dL in 69% of subjects by Day 28, reduced mean serum LH levels by approximately 90%, confirming that the therapeutic effect is achieved by inhibiting LH release, and reduced serum PSA levels.	achievement and maintenance of castrate testosterone levels have been the basis for the FDA approvals of other depot formulations of leuprolide. This trial design was agreed on by FDA and follows principles outlined in FDA guidance.
Risk and Risk Management	• The overall pattern of AEs reported in FP01C-13-001 is consistent with that expected in men in the demographic group and the disease under study, and are consistent with toxicities reported in published clinical trials and post-marketing reports of leuprolide. • The most common (>10%) adverse reactions, including laboratory abnormalities, were hot flush, decreased hemoglobin, hypertension, increased blood glucose, injection site reactions, upper respiratory tract infections, musculoskeletal pain, fatigue, and pain in extremity. • Warnings and Precautions included in Section 5 of product labeling for Camcevi include tumor flare, hyperglycemia and diabetes, cardiovasculat disease, QT/QTc prolongation, convulsions, and embryo-fetal toxicity. • No REMS is required for this application.	The safety profile is acceptable for the intended population. Extensive clinical experience exists with leuprolide products in the intended population. The package insert will retain all Warnings and Precautions in the package inserts for other leuprolide products.

1.4 Patient Experience Data

No patient experience data was submitted with this application.

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:						Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as					[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)			
			□	Observer reported outcome (ObsRO)			
			□	Clinician reported outcome (ClinRO)			
			□	Performance outcome (PerfO)			
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)					
	□	Patient-focused drug development or other stakeholder meeting summary reports					[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data					
	□	Natural history studies					
	□	Patient preference studies (e.g., submitted studies or scientific publications)					
	□	Other: (Please specify)					
□	Patient experience data that was not submitted in the application, but was considered in this review.						

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:
The Applicant's leuprolide mesylate injectable suspension (LMIS) 50 mg (Camcevi™ 42 mg) contains leuprolide mesylate equivalent to 42 mg leuprolide base. Leuprolide is a synthetic nonapeptide gonadotropin releasing hormone (GnRH) analogue (ATC code: L02A E02 [gonadotropin releasing hormone analogues]).

LMIS 50 mg (Camcevi™ 42 mg) is proposed for the treatment of (b) (4) advanced prostate cancer (b) (4) .

Prostate cancer is one of the leading causes of deaths in men globally. Men aged 65 years or older are the major group at risk; other common risk factors include ethnicity, family history, dietary habits, smoking, and occupational exposure (ACS 2013; Crocetti, 2015; ENCR 2014; Jemal, 2011; Martins et al., 2015; Siegel et al., 2017).
Therapeutic choice for the treatment of prostate cancer is determined based on age, tumour grade and stage as well as other medical conditions. In conjunction with radiation and chemotherapy, hormonal therapy is widely used in the treatment of prostate cancer patients (Parker et al., 2015). Evidence suggests that disease progression of prostate cancer is highly dependent on androgen levels. Long term hormonal control helps to alleviate the growth of proliferating prostate cancer cells and may be beneficial to patient survival (Sasse et al., 2012; Tamburrino et al., 2012).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Prostate cancer is an androgen-dependent tumor in most men at the time of initial presentation. The goal of androgen deprivation therapy is to suppress serum androgen levels to those normally observed following bilateral surgical orchiectomy. Based on these considerations, the FDA has accepted the surrogate endpoint of serum testosterone suppression to castrate levels as primary evidence of efficacy for gonadotropin releasing hormone analogues. For this NDA, the Division indicated that the attainment of castration levels of testosterone by treatment Day 28 and maintained through Day 336 could constitute an adequate primary efficacy outcome (see Section 3.2 of this review for details).

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2.2 Analysis of Current Treatment Options

Apart from surgical interventions and radiotherapy, the development of androgen deprivation therapy (ADT) has been the mainstay of hormonal treatment for prostate cancer over the years. Various types of pharmaceutical agents have been developed for medical androgen deprivation, including GnRH agonists, GnRH antagonists, oestrogen agonists, and androgen inhibitors (Hoda et al., 2017; refer to NDA Module 2.5, Section 2.5.1).
The GnRH agonist leuprolide is a synthetic nonapeptide analogue of naturally occurring GnRH that, when given continuously at therapeutic doses, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. The analogue possesses greater potency than the natural hormone (Hoda et al., 2017; Periti et al., 2002; Sethi and Sanfilippo, 2009; refer to NDA Module 2.5, Section 2.5.1).
With continuous administration, there is eventual suppression of gonadotropin release within 2 to 4 weeks (Hoda et al., 2017; Sethi and Sanfilippo, 2009). In males, testosterone is reduced to castrate levels (below the established castrate threshold or ≤ 50 ng/dL; or as more recently proposed ≤ 20 ng/mL. Upon leuprolide cessation, androgen deprivation is reversible (Sethi and Sanfilippo, 2009; refer to NDA Module 2.5, Section 2.5.1).
The leuprolide-based hormonal ADT is the mainstay of treatment for locally advanced and metastatic prostate cancer, as well as for the adjuvant treatment of patients with intermediate-risk or high-risk localised prostate cancer. Leuprolide ADT has been shown to improve quality of life and prolong life in prostate carcinoma patients (Hoda et al., 2017; Sethi and Sanfilippo, 2009; refer to NDA Module 2.5, Section 2.5.1).

The clinical efficacy of the GnHR agonist leuprolide for the palliative treatment of advanced prostate carcinoma in patient in need for ADT has been established in three decades of clinical use (Hoda et al., 2017; Sethi and Sanfilippo, 2009; refer to NDA Module 2.5, Section 2.5.1), and a considerable number of leuprolide depot have been since introduced:
Leuprolide (as an acetate salt) has been approved for the palliative treatment of prostate cancer in the United States since 1985 (Lupron® Injection; NDA 019010; AbbVie, Inc.) (refer to NDA Module 2.5, Section 2.5.1). A considerable number of leuprolide drug products have been approved and marketed in the US, with the initial leuprolide acetate form, Lupron® 1 mg for daily administration, authorized three decades ago. Following leuprolide 1 mg forms requiring daily administration, prolonged-release leuprolide forms allowing for monthly, 3-monthly, and 6-monthly dosing (7.5 mg, 22.5 mg, and 45 mg leuprolide acetate forms [e.g. Eligard®]) have been introduced.

<u>The Applicant's Position:</u>
Camcevi™ 42 mg represents the first ready-to-use leuprolide prolonged-release pharmaceutical form (appropriate for 6 month dosing intervals), exhibiting the same anti androgenic capacity in prostate cancer patients while providing a comparable safety and

tolerability profile. In contrast to currently approved depot / prolonged-release leuprolide products, which require reconstitution prior to use, Camcevi™ 42 mg will be supplied as ready-to-use drug product (no premixing will be required prior to subcutaneous injection), pre-filled in a single, sterile syringe.
The proposed LMIS product differs from currently approved leuprolide products in that the salt used for the proposed drug product (mesylate) differs from that used in the currently approved products (acetate). Camcevi™ 42 mg is a pre mixed product containing 42 mg of leuprolide free base (~48 mg leuprolide mesylate) formulated in a solution of N-methyl-2-pyrrolidone (NMP) and poly (D,L-lactide) (PLA). The difference in salt weight has been accounted for so that the free base equivalent is the same between the proposed Camcevi™ 42 mg drug product and the currently approved 45 mg leuprolide acetate products (refer to NDA Module 2.5, Section 2.5.1).

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as Listed Drug.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Because Camcevi is a mesylate salt and all other marketed leuprolide products are acetate salts, and because both mesylate and acetate leuprolide products may be used as ADT in patients with prostate cancer, it is important that the drug strength be expressed in a manner that minimizes the potential for medication errors. In marketed leuprolide acetate products, 45 mg contains 42 mg of the free base form of leuprolide, whereas with leuprolide mesylate, 48 mg contains 42 mg of the free base form of leuprolide. Current USP nomenclature policy directs that strength of drugs be named according to their freebase forms rather than salt forms. The Camcevi Prescribing Information will therefore present the recommended dosage of leuprolide injectable emulsion as 42 mg subcutaneously every 6 months. See Section 6.2 of this review for additional details.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

There have been 5 different non-generic leuprolide drug products approved by the FDA for the palliative treatment of prostate cancer. The approved products are Eligard®, Lupron/Lupron Depot®, Leuprolide Acetate, Lupaneta® pack, and Viadur®. All FDA-approved leuprolide drug products are leuprolide acetate (leuprorelin). There are currently no leuprolide mesylate drug products approved in the United States.

The first approved leuprolide product (Lupron®, NDA 019010-001) was approved in 1985 for the palliative treatment of advanced prostatic cancer. This initially approved leuprolide drug product, and most of the early leuprolide products, required daily subcutaneous or intramuscular injections at 1.0 mg. In 1990, the first of the monthly leuprolide depot injection products was approved by the FDA (NDA 020011), and leuprolide is currently available in 1-month (7.5 mg), 3-month (22.5 mg), 4-month (30 mg), and 6-month (45 mg) depot dosages. A 12-month subcutaneous implant was developed and approved by the FDA in 2000 for the treatment of locally advanced or metastatic prostate cancer (NDA 021088), however the drug product was discontinued by the manufacturer in 2007 and the NDA offically withdrawn in 2011.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of the key regulatory milestone are presented below:

Date	Regulatory Milestone and Details
10 November 2008	Pre IND Meeting: Foresee will rely on Lupron® (NDA 019010) to support approval of the proposed LMIS 50 mg application via that 505(b)(2) regulatory pathway.
14 April 2014	IND submission/Study may proceed 15 May 2015
06 August 2016	Type C (WRO)- Sponsor proposal for the CMC, nonclinical, and clinical data intended to support a submission via the NDA 505(b) (2) pathway
23 October 2017	Pre-NDA Meeting- Sponsor proposal for the NDA content and format to support an NDA submission
25 July 2019	Type A-Meeting to discuss the issues identified in the Refuse to File letter dated May 23, 2019
27 July 2020	NDA resubmission

The FDA's Assessment:

The FDA agrees with the Applicant's summary of pre-submission regulatory events. IND 103206 for leuprolide injectable emulsion opened 6 August 2008. At a Pre-IND Meeting 10 November 2008, the FDA agreed that the results of a single phase 3 clinical study with a sole efficacy

endpoint of the percentage of patients who attain serum castration testosterone levels by Day 29 and maintained such levels at every assessment through the full treatment period could potentially be sufficient to satisfy the efficacy requirements for a 505(b)(2) NDA. For the primary analysis, the FDA recommended using a confidence interval approach, with a two-sided 95% CI having a lower bound of at least 90%. At pre-NDA meeting on 23 October 2017, the FDA stated that a 505(b)(2) application would be an acceptable approach to an NDA, with clinical efficacy data from FP01C-13-001 and nonclinical and clinical safety data from Sponsor-conducted studies and information in published literature.

NDA 211488 opened 28 March 2019. On May 23, 2019, the FDA issued a Refuse to File decision for the initial submission of NDA 211488. The device constituent parts of the combination product were not accepted for filing because the Applicant was unable to provide test protocols and reports verifying that these met essential performance requirements (EPRs) for dose accuracy, break loose force, and glide force. The FDA indicated that to allow filing of their NDA, the Applicant would need to provide design verification data on the final finished combination product, including test protocols and reports for the EPRs using an appropriate sample size to achieve a 95% confidence interval, and provide stability testing to demonstrate that device EPRs are within specification at the end of the claimed shelf life.

The Applicant resubmitted their NDA on 27 July 2020, and on 7 October 2020, the FDA notified the Applicant that the application had been filed and that the filing review had identified no potential issues that would prevent filing.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Three investigators, Dr. Jeffrey Frankel (Site US03), Dr Eliot Horowitz (Site US01), and Dr. Mark Deguenther (Site US07), were selected for clinical inspection. The inspection of Dr. Frankel found no regulatory violations, and the Applicant's submitted data were verifiable with source data at the investigator site. For Drs. Horowitz and Deguenther, the intended inspections could not be conducted due to COVID-19 pandemic-related travel restriction status at the two investigator sites. After review of the overall efficacy and safety findings with no major review issues identified that were unresolved and/or that would potentially have required further investigation with site inspections, DO1 decided to forgo these final two inspections for the current submission. Based on the available inspection results, the clinical data generated from Dr. Frankel appear reliable in support of this 505(b)(2) NDA.

4.2 Product Quality

Leuprolide is a gonadotropin releasing hormone (GnRH) agonist for the palliative treatment of advanced prostate cancer. Leuprolide is a synthetic nonapeptide analog of naturally occurring GnRH that inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. Foresee Pharmaceuticals resubmitted 505(b)(2) NDA for CAMCEVI (leuprolide mesylate injectable emulsion) after refuse to file (RTF) of its original submission dated Mar 28, 2019 based on the deficiencies from the CDRH review of the device. The applicant conducted a Phase 3 study to demonstrate the safety and efficacy of its proposed drug. The applicant will also rely on the FDA's finding of nonclinical safety of the Listed Drug (NDA 19010) that was approved for marketing in 1985. The proposed product differs from the currently approved leuprolide products in the salt form of the drug substance (proposed drug is leuprolide mesylate vs the marketed leuprolide acetate). The strength of the proposed drug (42 mg of API) is the same as the marketed leuprolide drugs when calculated on free base basis. The proposed product is a depot formulation which releases leuprolide over a 6-month period after a single subcutaneous administration. Unlike currently marketed leuprolide products that require reconstitution and/or mixing prior to administration, the proposed product will be supplied as ready-to-use in a sterile, pre-filled syringe along with a sterile 18 gauge needle. The product quality review team found the CMC information in the NDA acceptable. The manufacturing and controls facilities are deemed acceptable based on Office of Pharmaceutical Manufacturing Assessment (OPMA) review recommendation.

4.3 Clinical Microbiology

CAMCEVI is manufactured by (b) (4). The microbiology review assessed sterility assurance of the drug product manufacturing and specifications for sterility and endotoxins. All the information are deemed adequate.

4.4 Devices and Companion Diagnostic Issues

The FDA Center for Devices and Radiological Health/Office of Product Evaluation and Quality reviewed this application in collaboration with CDER and concluded that the device constituent parts of the combination product are approvable. The review noted that the design verification results obtained on a statistically valid sample confirm that leuprolide injectable emulsion 50 mg drug-device combination product performs correctly to achieve final user needs in terms of dose accuracy, break loose force and glide force, and results of deliverable weight in container, break loose force and glide force obtained during drug product development show that device constituents deliver intended dose in reproducible and accurate manner and functionality of leuprolide injectable emulsion is maintained throughout drug product shelf-life.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Camcevi is a gonadotropin-releasing hormone (GnRH) agonist. Camcevi is a sterile formulation of leuprolide mesylate for subcutaneous injection. The Applicant submitted this NDA submission as a 505(b)(2) application for the same indication as the listed drug Lupron injection (leuprolide acetate; NDA 019010). The Applicant proposed to rely on FDA's previous findings of nonclinical safety for the listed drug by providing clinical bridging data. This submission is a complete resubmission of the original NDA submission dated March 28, 2019 for which FDA issued a Refuse to File Letter on May 23, 2019. No nonclinical pharmacology/toxicology filing issues were identified at the time of the original NDA submission, and no new nonclinical pharmacology/toxicology data were submitted in this NDA resubmission.

In support of this NDA submission, the Applicant conducted pharmacokinetic and GLP-compliant single-dose 3- and 6-month toxicology studies with leuprolide mesylate injectable suspension (LMIS) and Eligard, a sterile polymeric matrix formulation of leuprolide acetate. In these studies, male Sprague-Dawley rats were administered a single subcutaneous dose of saline, vehicle control or 6.8 mg, 20.3 mg, 33.8 mg LMIS, or 30 mg Eligard. The toxicology studies with LMIS did not identify any new toxicity findings which were not expected based on the mechanism of action of LMIS and the toxicity profile of Lupron, and no significant differences in pharmacokinetic and toxicokinetic parameters were observed. The target organs of toxicity for LMIS were the pituitary (hypertrophy and hyperplasia) and male reproductive organs, including the epididymis (oligospermia), prostate (atrophy/decreased luminal secretion), seminal vesicles, and testes (atrophy/degeneration of the seminiferous tubules and/or germ cell depletion). Additional findings included shortening of prothrombin time and increased alkaline phosphate levels (6-month study only) in all LMIS and Eligard-treated groups. Administration of LMIS resulted in decreases in group mean serum testosterone concentration to castrate levels (below 50 ng/dL or 0.500 ng/mL), and the testosterone suppression was generally maintained through Day 183 following a single dose administration.

The labeling for Camcevi is consistent with that from Lupron, with no major changes except for conversion to the Pregnancy and Lactation Labeling Rule (PLLR) format. Overall, the nonclinical data submitted to this NDA are adequate to support the approval of Camcevi for the proposed indication as a 505(b)(2) NDA, based on the adequacy of the clinical pharmacokinetic and safety data as the scientific bridge for the reliance of the nonclinical information for the listed drug Lupron.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:
The following files were referred to in the LMIS NDA by the Sponsor:
DMF (b) (4)

5.3 Pharmacology

Primary pharmacology

The FDA's Assessment:

The Applicant did not submit any pharmacology studies with leuprolide injectable emulsion in this NDA submission. The Applicant conducted a pharmacokinetic/pharmacodynamic study in rats to demonstrate the pharmacological action of leuprolide injectable emulsion. This study was reviewed under the ADME/PK section of this review. Additional supportive primary pharmacodynamics of leuprolide acetate from the listed drug labeling and published literature was summarized in the NDA submission. The information from published literature was not needed to support approval of this NDA submission.

Secondary Pharmacology

The Applicant's Position:
No secondary pharmacology studies have been conducted with leuprolide mesylate or LMIS 50 mg. LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference listed drug (LD) (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100). As the present NDA relies on the Agency´s finding of safety and/or effectiveness and the approved label for the identified LD no further data has been generated.

The FDA's Assessment:
FDA agrees that the Applicant did not submit any primary or secondary pharmacology studies with leuprolide injectable emulsion in this NDA submission. The Applicant provided clinical pharmacokinetic and safety data as the scientific bridge for the reliance of the nonclinical information for the listed drug Lupron.

Safety Pharmacology

The Applicant's Position:
No dedicated safety pharmacology studies have been conducted with leuprolide mesylate or LMIS 50 mg. In the completed 28 day, 3 month and 6 month single dose subcutaneous toxicity studies no test article related clinical observations and differences between the LMIS 50 mg (clinical formulation) and the comparator Eligard® 45 mg were reported (Study FP01N-12-007; Study FP01N-13-001; FP01N-13-004; refer to NDA Module 2.6.6 Section 2 and NDA Module 2.6.7).
LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference listed drug (LD) (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100) and intends to rely on the Agency's findings of nonclinical and clinical safety/effectiveness and the approved label for the LD.

The FDA's Assessment:
FDA agrees that the Applicant did not conduct or submit any standalone safety pharmacology studies with leuprolide injectable emulsion. Based on ICH S9 Guidance, these studies were not warranted to support clinical trials or a marketing application in the proposed patient population. Vital organ functions were evaluated in the toxicology studies with leuprolide injectable emulsion. FDA agrees with the Applicant's conclusion that there were no significant findings or differences in drug-related effects on vital organ functions between leuprolide injectable emulsion and Eligard.

5.4 ADME/PK

The Applicant's Position:
Single dose subcutaneous studies were conducted in male rats to characterize the pharmacokinetics/toxicokinetics (PK/TK) of leuprolide and the correlating testosterone levels (pharmacodynamic (PD) surrogate) using a method which was developed for their simultaneous determination in rat serum. A PK/PD study evaluating various formulations of LMIS 50 mg with a follow-up period of approximately 6 months indicated comparable PK/PD profiles of LMIS 50 mg formulations and Eligard® 45 mg (Study FP01N-11-001; refer to NDA Module 2.6.4 Section 3).
In the single dose subcutaneous toxicity studies that utilized the clinical formulation of LMIS 50 mg the same dose levels were used but were followed up post dose for different durations (28 days, 3 months, and 6 months, respectively (Study FP01N-12-007; Study FP01N-13-001; FP01N-13-004; refer to NDA Module 2.6.6 Section 2 and Module 2.6.7). Eligard® 45 mg

was included as a comparator to the LMIS 50 mg high dose group. Three month and 6 month studies were conducted in compliance with GLP. Dose proportionality across all doses was demonstrated in the 6-month study but not in the 28-day or 3-month studies. This was attributed in part to the different drug release rates for the different doses, as the lower doses tended to release drug slower than the high dose when dosed less than the 6 months required for full release. Overall, similar pharmacokinetics and androgen ablation efficacy between LMIS 50 mg high dose and Eligard® 45 mg was demonstrated.
No distribution, metabolism, or excretion and PK interaction studies have been conducted for LMIS 50 mg.
LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as as LD (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100). As the present NDA relies on the Agency´s finding of safety and/or effectiveness and the approved label for the identified LD no further data has been generated.

The FDA's Assessment:
FDA generally agrees with the Applicant's conclusion of the study results. Additional noteworthy study data, TK data and comments on Applicant's summary are provided below.

Data (presented by FDA)

TK data from general toxicology studies

Three month toxicology study in rats (Study # FP01N-13-001)

Dose proportionality: approximately dose proportional from 6.8 – 33.8 mg LMIS

Parameters	6.8 mg LMIS	20.3 mg LMIS	33.8 mg LMIS	30.0 mg Eligard
T_{max} (h)	4.0	2184	4.0	4.0
C_{max} (ng/mL)	31.8	98.3	132	345
DNC_{max}[a]	5.49	5.65	4.54	12.3
$AUC_{0\text{-}182d}$ (d·ng/mL)	308	2186	2819	2431
$DNAUC_{0\text{-}182d}$[a]	53.1	126	97.2	86.8

[a] Normalized by dose (leuprolide free base)

Six month toxicology studies in rats (Study # FP01N-13-004)

Dose proportionality: approximately dose proportional from 6.8 – 33.8 mg LMIS

Parameters	6.8 mg LMIS	20.3 mg LMIS	33.8 mg LMIS	30.0 mg Eligard
T_{max} (h)	4.0	4	4	4
C_{max} (ng/mL)	50	161	316	308
DNC_{max}[a]	9	9	11	11
$AUC_{0\text{-}91d}$ (d·ng/mL)	1047	3189	4383	4519
$DNAUC_{0\text{-}91d}$[a]	181	183	151	161

[a] Normalized by dose (leuprolide free base)

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

Three single dose subcutaneous toxicity studies were conducted in rats using doses of 6.8, 20.3, and 33.8 mg/animal of LMIS 50 mg (clinical formulation) (Study FP01N-12-007; Study FP01N-13-001; FP01N-13-004; refer to NDA Module 2.6.6 Section 2 and NDA Module 2.6.7). The animals were followed up for 28 days, 3 months, or 6 months. Only male rats were used since the proposed clinical indication is limited to male patients. Eligard® 45 mg was included as a comparator to the LMIS 50 mg high dose group. Three month and 6 month studies were conducted in compliance with GLP.

In all three studies, no LMIS 50 mg related changes were identified in clinical observations (including the injection site), haematology, clinical chemistry, and urinalysis. As expected, considering the PD effects of leuprolide, reduced size and weight of the male sex organs (testes, epididymides, prostate/seminal vesicles) was seen following treatment in all leuprolide groups, including the comarator group (Eligard® 45 mg). These effects were not considered adverse, since they were related to the pharmacology of the test articles.

When treated with leuprolide for 28 days, no treatment-related adverse effects were noted in any group, and the NOAEL was the highest dose tested of 33.8 mg/animal. When treated with leuprolide for ≥ 3 months, kidney size was also reduced, and pituitary hyperplasia was observed at all dose levels and with Eligard® 45 mg. Severity correlated with increasing dose levels only in the 3 month study. The pituitary hyperplasia occurred at a similar incidence at all dose levels and in the Eligard® 45 mg reference group and was considered adverse; therefore, a NOAEL was not established in this study. After 6 months of leuprolide treatment, a few animals experienced clinical decline from the pituitary changes (pituitary hyperplasia and adenoma), which led to the early termination of one animal in the 6.8 mg/kg group. The pituitary effects were considered adverse and occurred at the lowest dose of 6.8 mg/animal; therefore, a

NOAEL was not established in this study. However, similar effects were noted in the Eligard® 45 mg group, demonstrating that leuprolide mesylate does not cause any additional toxicological effects.

No repeat dose toxicity studies were conducted for leuprolide mesylate of LMIS 50 mg. LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference listed drug (LD) (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100). As the present NDA relies on the Agency´s finding of safety and/or effectiveness and the approved label for the identified LD no further data has been generated.

The FDA's Assessment:
FDA generally agrees with the Applicant's conclusion of the study results for the single-dose 3- and 6-month studies. The single-dose 28-day study was not conducted under GLP-compliance and was not reviewed for this NDA submission. FDA analysis of the study data from the 3- and 6-month toxicology studies is provided below.

Data (presented by FDA)

Study title/ number: Leuprolide mesylate for injectable suspension 50 MG (LMIS 50 MG): A 3-month single subcutaneous dose toxicity study in rats (GLP)/ FP01N-13-001

- Target organs of toxicity included the pituitary (hypertrophy and hyperplasia) and male reproductive organs, including the epididymis (oligospermia), prostate (atrophy/decreased luminal secretion), seminal vesicles, and testes (atrophy/degeneration of the seminiferous tubules).
- Shortening of prothrombin time were observed in all LMIS and Eligard-treated groups.
- Similar findings were observed in LMIS- and Eligard-treated groups.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (saline), 0 (vehicle control), 6.8, 20.3, 33.8 mg LMIS (based on leuprolide salt), or 30 mg Eligard
Route of administration:	Subcutaneous injection (on dorsal thoracis region under isofluorane anesthesia)

Formulation/Vehicle:	Poly (D,L-lactide) solution in N-methylpyrrolidone (NMP)
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	10 (males only)
Age:	7 weeks old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	No significant changes in body weights or body weight gains were noted.
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Coagulation	Shortening of PT was noted in all leuprolide-treated groups revealing 9%, 10%, 12% and 11% reduction compared to vehicle control for the 6.8 mg, 20.3 mg, 33.8 mg, and 30 mg Eligard groups, respectively. The changes at ≥ 20.3 mg were statistically significant compared to the vehicle control group.
Clinical Chemistry	No significant drug-related findings were noted.
Urinalysis	Unremarkable
Gross Pathology	

(# Animals/Group)	Dosing Groups					
	Saline Control (10)	Vehicle Control (10)	6.8 mg LMIS (10)	20.3 mg LMIS (10)	33.8 mg LMIS (10)	30.0 mg Eligard (10)
Epididymis						
Decrease size						
Minimal	0	0	2	2	1	1*
Mild	0	0	3	4	5	2
Moderate	0	0	0	1	1	2
Severe	0	0	0	0	0	1*
Prostate						
Decreased size						
Minimal	0	0	0	0	0	1
Mild	0	0	3	4	3	0
Moderate	0	0	1	2	2	1
Severe	0	0	0	1	1	3
Seminal vesicles						
Decreased size						
Minimal	0	0	0	0	0	1
Mild	0	0	2	3	1	1
Moderate	0	0	3	1	5	0
Severe	0	0	0	5	2	3
Marked	0	0	0	0	0	1
Testes						
Decrease size						
Minimal	0	0	4	1	1	2
Mild	0	0	4	7	3	2
Moderate	0	0	2	1	4	1
Severe	0	0	0	0	1	3
Marked	0	0	0	0	0	1

* Lesion(s) occurred at different severity levels on the 2 sides of one animal (1059)

Organ Weights	Decreases in group mean testicular (-38% to -46% of vehicle control) and epididymal (-34% to -45% of vehicle control) weights were noted in all LMIS- and Eligard-treated groups. Decreased testicular and epididymal weights were similar between the 33.8 mg LMIS and the 30.0 mg Eligard groups.
Histopathology Adequate battery: Yes	

(# Animals/Group)	Dosing Groups					
	Saline Control (20)	Vehicle Control (19)	6.8 mg LMIS (19)	20.3 mg LMIS (20)	33.8 mg LMIS (20)	30.0 mg Eligard (20)
Epididymis						
Oligospermia						
Minimal	0	0	4	4	2	0
Mild	0	0	1	0	3	1
Moderate	0	0	0	2	0	1
Severe	0	0	0	0	0	1
Marked	0	0	0	0	1	2
Pituitary						
Hypertrophy/hyperplasia, basophils						
Minimal	0	0	4	3	5	5
Mild	0	0	1	0	1	0
Moderate	0	0	0	0	0	1
Focal (nodular) hyperplasia, basophils						
Minimal	0	0	4	5	1	4
Mild	0	0	0	2	1	0
Moderate	0	0	2	1	0	0
Focal (nodular) hyperplasia with atypia, basophils						
Moderate	0	0	0	0	0	1
Prostate						
Atrophy/decreased luminal secretion						
Minimal	0	0	0	1	2	3
Mild	0	0	0	0	1	2
Moderate	0	0	2	3	2	0
Severe	0	0	2	3	4	3
Marked	0	0	0	1	1	1
Seminal vesicles						
Atrophy/decreased luminal secretion						
Minimal	0	0	0	0	1	1
Mild	0	0	0	2	2	3
Moderate	0	0	2	2	1	1
Severe	0	0	2	2	3	1
Marked	0	0	1	3	3	3
Testes						
Atrophy/degeneration, seminiferous tubules						
Minimal	0	0	4	5	6	4
Mild	0	0	3	2	3	3
Moderate	0	0	0	0	0	1

Severe	0	0	0	0	1	1
Hypospermatogenesis						
Minimal	0	0	1	4	0	0
Mild	0	0	1	2	0	0
Moderate	0	0	0	0	0	1
Severe	0	0	0	0	0	1
Marked	0	0	0	0	1	0

Serum Testosterone Evaluation	Mean group mean (n = 5) serum testosterone concentration decreased to castrate levels (below 50 ng/dL or 0.500 ng/mL) in all LMIS- and Eligard-treated groups starting on Day 43, Day 29, Day 22, or Day 15 for 6.8 mg LMIS, 20.3 mg LMIS, 33.9 mg LMIS, and 30.0 mg Eligard groups, respectively. Testosterone suppression was generally maintained through Day 92. Sporadic increases of testosterone were observed above castrate levels in the 30.0 mg Eligard group (on Days 22, 43, 71).

-: indicates reduction in parameters compared to control.

Study title/ number: Leuprolide mesylate for injectable suspension 50 MG (LMIS 50 MG): A 6-month single subcutaneous dose toxicity study in rats (GLP)/ FP01N-13-004

- Target organs of toxicity included the pituitary (hypertrophy and hyperplasia) and male reproductive organs, including the epididymis (oligospermia), prostate (atrophy/decreased luminal secretion), seminal vesicles, and testes (tubular atrophy and germ cell depletion).
- Shortening of prothrombin time were observed in all LMIS and Eligard-treated groups.
- Similar findings were observed in LMIS- and Eligard-treated groups.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (saline), 0 (vehicle), 6.8 mg, 20.3 mg, 33.8 mg LMIS (based on leuprolide salt), or 30 mg Eligard
Route of administration:	Subcutaneous injection (on dorsal thoracis region under isofluorane anesthesia)
Formulation/Vehicle:	Poly (D,L-lactide) solution in N-methylpyrrolidone (NMP)
Species/Strain:	Rat/Sprague-Dawley

Number/Sex/Group:	20
Age:	9 weeks old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One vehicle control animal (Animal No. 1021) and one 6.8 mg LMIS animal (Animal No. 1059) were euthanized on Days 137 and 181, respectively. Animal No. 1021 was noted with body weight loss, emaciation and increased urine glucose and high ketone levels on urinalysis (indicative of diabetes). Animal No. 1059 was noted with weight loss, decreased food consumption, clinical signs (palpebral closure, decreased activity, hunched posture, dehydration, emaciation, piloerection, and red secretion from nose), pituitary adenoma.
Clinical Signs	6.8 mg LMIS: palpebral closure, hunched posture, piloerection, decreased activity, emaciation, red discharge from nose, and dehydration. 20.3 mg LMIS: injection site abrasion 30 mg Eligard: injection site abrasion
Body Weights	33.8 mg LMIS: ≥ -9% of vehicle control on Days 57 – 183 30 mg Eligard: ≥ -9% of vehicle control on Days 64 – 183 All LMIS- or Eligard-treated animals showed decreased body weight gains of -18% to -25% of vehicle control on Day 183.
Ophthalmoscopy	Unremarkable
Hematology	

Changes in hematology parameters (% of vehicle control)

	Dose Levels				
	Saline Control	6.8 mg LMIS	20.3 mg LMIS	33.8 mg LMIS	30.0 mg Eligard
Red blood cells	2	-4	-7***	-4*	-4
MCV	1	4**	6**	4**	4**
MCH	0	6***	8***	5***	5***
MCHC	-1	2**	1	1*	1*

* Statistically significant, $p < 0.05$ by Dunnett's LSD test or Dunn's test
** Statistically significant, $p < 0.01$ by Dunnett's LSD test
*** Statistically significant, $p < 0.001$ by Dunn's test

Coagulation	

Changes in coagulation parameters (% of vehicle control)

	Dose Levels				
	Saline Control	6.8 mg LMIS	20.3 mg LMIS	33.8 mg LMIS	30.0 mg Eligard
PT	0	-24***	-22***	-21***	-21***
APTT	2	-4	-3	3	-7

*** Statistically significant, $p < 0.001$ by Dunn's test

Clinical Chemistry	

Changes in clinical chemistry parameters (% of vehicle control)

	Dose Levels				
	Saline Control	6.8 mg LMIS	20.3 mg LMIS	33.8 mg LMIS	30.0 mg Eligard
ALP	-2	-38***	-27**	-27**	-28**
Na	0	0	1	2**	2**
K	3	-9	-3	-13**	-13**
Cl	0	1	2*	2**	3*
P	4	-8	-7	-3	-10*
Cholesterol	-13	27*	24	36**	16

* Statistically significant, $p < 0.05$ by Dunnett's LSD test
** Statistically significant, $p < 0.01$ by Dunnett's LSD test or Dunn's test
*** Statistically significant, $p < 0.001$ by Dunn's test

Urinalysis	Unremarkable
Gross Pathology	

(# Animals/Group)	Dosing Groups					
	Saline Control (20)	Vehicle Control (19)	6.8 mg LMIS (19)	20.3 mg LMIS (20)	33.8 mg LMIS (20)	30.0 mg Eligard (20)
Epididymis						
Decrease size						
Minimal	0	0	5	1	3	4
Mild	0	0	4	8	7	2
Moderate	0	0	5	8	1	3
Severe	0	0	1	1	2	0
Pituitary						
Enlargement						
Minimal	0	0	1	0	0	1
Mild	0	0	0	1	0	0
Nodule						
Present	0	0	1	1	1	2
Mass(es)						
Present	0	0	9	4	6	4
Prostate						
Decreased size						
Minimal	0	0	3	3	3	1
Mild	0	0	3	4	2	5
Moderate	0	0	5	8	5	7
Severe	0	0	2	3	1	3
Seminal vesicles						
Decreased size						
Minimal	0	1	3	3	3	1
Mild	0	0	3	4	2	5
Moderate	0	0	5	8	5	7
Severe	0	0	2	3	1	3
Testis						
Decrease size						
Minimal	0	0	1	0	2	0
Mild	0	0	14	12	13	14
Moderate	0	0	3	7	2	4
Severe	0	0	1	1	2	0

Organ Weights

Changes (%) in organ weights relative to vehicle control group

	Dosing Groups				
	Saline Control	**6.8 mg LMIS**	**20.3 mg LMIS**	**33.8 mg LMIS**	**30.0 mg Eligard**
Epididymis					
Organ Weight	-6	-40**	-46**	-41**	-28**
Organ Weight/Brain Weight	-4	-38**	-44**	-39**	-26**
Organ Weight/Body Weight	-3	-34**	-41**	-34**	-20**
Heart					
Organ Weight	-3	-23**	-16**	-17**	-20**
Organ Weight/Brain Weight	-1	-21***	-15*	-15**	-18***
Organ Weight/Body Weight	0	-15**	-9*	-7	-12**
Kidney					
Organ Weight	-1	-19**	-17**	-20**	-20**
Organ Weight/Brain Weight	1	-17**	-16**	-18**	-18**
Organ Weight/Body Weight	2	-11**	-11**	-11**	-11**
Liver					
Organ Weight	-2	-19**	-17**	-20**	-20**
Organ Weight/Brain Weight	0	-17**	-16**	-18**	-18**
Organ Weight/Body Weight	2	-11**	-11**	-11**	-11**
Pituitary					
Organ Weight	-3	331*	50	176	111
Organ Weight/Brain Weight	-1	336*	55	188*	120
Organ Weight/Body Weight	0	412***	61	207***	127
Testis					
Organ Weight	-2	-41**	-46**	-42**	-38**
Organ Weight/Brain Weight	0	-40**	-45**	-40**	-36**
Organ Weight/Body Weight	1	-36**	-42**	-36**	-32**

* Statistically significant, $p < 0.05$ by Dunnett's LSD test or Dunn's test
** Statistically significant, $p < 0.01$ by Dunnett's LSD test
*** Statistically significant, $p < 0.001$ by Dunn's test

Histopathology
Adequate battery: Yes

(# Animals/Group)	Dosing Groups					
	Saline Control (20)	Vehicle Control (19)	6.8 mg LMIS (19)	20.3 mg LMIS (20)	33.8 mg LMIS (20)	30.0 mg Eligard (20)
Epididymis						
Reduced luminal sperm						
Minimal	0	0	6	7	4	1
Mild	0	0	1	3	2	2
Moderate	0	0	1	3	0	1
Severe	1	1	2	0	1	1
Marked	0	0	1	1	2	0
Pituitary						
Focal hyperplasia						
Minimal	0	2	2	4	5	6
Mild	0	0	1	5	4	6
Moderate	0	0	2	1	3	2
Severe	0	0	2	3	0	1
Adenoma	0	0	8	5	8	4
Prostate						
Decreased luminal secretion						
Minimal	0	0	2	3	1	1
Mild	0	0	0	3	7	3
Moderate	0	0	3	5	4	3
Severe	0	0	5	3	1	10
Marked	0	0	3	4	3	2
Seminal vesicles						
Decreased luminal secretion						
Minimal	0	0	2	2	0	0
Mild	0	0	0	4	6	4
Moderate	0	0	3	5	4	5
Severe	0	0	5	3	3	6
Marked	0	0	3	4	3	4
Testis						
Germ cell depletion						
Minimal	0	0	12	10	6	7
Mild	0	0	1	7	5	6
Moderate	0	0	1	0	3	0
Marked	0	0	0	1	0	0
Tubular atrophy						
Minimal	0	0	2	3	2	9
Mild	0	0	3	2	1	0
Marked	1	1	2	0	1	0

Serum Testosterone Evaluation	Mean group mean serum testosterone concentration decreased to castrate levels (below 50 ng/dL or 0.500 ng/mL) in all LMIS- and Eligard-treated groups starting on Day 15, and the testosterone suppression was generally maintained through Day 183. Sporadic increases of testosterone were observed above castrate levels at 6.8 mg LMIS but not in the other LMIS- or Eligard-treated groups.
[If a table is to be included, insert it in this row]	

-: indicates reduction in parameters compared to control.

5.5.2 Genetic Toxicology

The Applicant's Position:

No gentotoxicity/mutagenicity studies were conducted with leuprolide mesylate or LMIS 50 mg. LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injectio n1 mg as LD (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100). As the present NDA relies on the Agency´s finding of safety and/or effectiveness and the approved label for the identified LD no further data has been generated.

The FDA's Assessment:

FDA agrees.

5.5.3 Carcinogenicity

The Applicant's Position:

No carcinogenicity studies were conducted with leuprolide mesylate or LMIS 50 mg.
LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference LD (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100). As the present NDA relies on the Agency´s finding of safety and/or effectiveness and the approved label for the identified LD no further data has been generated.

The FDA's Assessment:

FDA agrees.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:
No reproductive and developmental toxicity studies were conducted.
LMIS 50 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference LD (NDA 019010; AbbVie, Inc.). The Applicant established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100). As the present NDA relies on the Agency´s finding of safety and/or effectiveness and the approved label for the identified LD no further data has been generated.

The FDA's Assessment:
FDA agrees.

5.5.5 Other Toxicology Studies

The Applicant's Position:
Impurities: Shelf life specifications for impurity (b) (4), which are major impurities of LMIS 50 mg drug product, were qualified by both the 3- and 6-month single dose toxicity studies (refer to NDA Module 2.4 Section 1.3.2).

Excipients: All of the excipients of the proposed drug product are already contained in FDA-approved products and/or are reported to be safe at the doses expected to be given (refer to NDA Module 2.6.6 Section 7 and NDA Module 2.4 Section 1.3.1).

The FDA's Assessment:
Based on the information provided by the CMC review team, the specific impurities D-Ser-leuprolide, D-His-leuprolide, and L-Leu-leuprolide were below the acceptance criteria set in the USP monograph for leuprolide acetate. The sponsor proposed an acceptance criteria of (b) (4) ppm for (b) (4) impurities, based on the acceptable total daily intake recommended in the ICH M7 guidance, which is also acceptable from the perspective of the nonclinical pharmacology/toxicology discipline.

The CMC review team also requested nonclinical input on the Applicant's toxicology assessments of identified extractable and leachables - (b) (4), with estimated exposure or safety concern threshold of (b) (4), respectively. The TDI of all extractables and leachables was below the acceptable TDI of 120 µg/day for up to 30 dosing days outlined in the ICH M7 guidance, based on intermittent dosing

of once every 6 months. While ICH M7 is not applicable to patient populations within the scope of ICH S9 and ICH S9 Q&A, applying a more conservative approach is not necessary for the proposed patient population. In addition, the TDI for extractables and leachables are below the qualification limits recommended in ICH Q3 guidances. While these guidances are not entirely applicable to extractables and leachables, the principles can be applied given the patient population, low systemic exposure, and intermittent administration. Thus overall, there are no safety concerns with these extractables and leachables from the manufacturing process or container closure system.

X	X
Haw-Jyh Chiu Primary Reviewer	Tiffany Ricks Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:
Leuprolide is a gonadotropin-releasing hormone (GnRH) agonist acts as a potent inhibitor of gonadotropin secretion. The Applicant is seeking approval of Leuprolide Mesylate Injectable Suspension Camcevi™ 42 mg (LMIS 50 mg) via 505(b)(2) regulatory pathway with Lupron® Injection 1 mg as the reference (NDA 019010; AbbVie, Inc.). The proposed leuprolide dosing regimen is 42 mg every 6 months via subcuteaneous (SC) injection.

The clinical pharmacology review focuses on the evaluation of appropriateness of the proposed dose. The dosing regimen is supported by the PK-PD relationship, i.e., leuprolide-testosterone concentration profile, as well as safety and efficacy evidence from Study FP01C-13-001.

6.1.1 Recommendations

The Clinical Pharmacology review team has reviewed the information contained in NDA 211488. The application is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and/or comments are summarized below:

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	A multicenter, open-label, single-arm trial (Study FP01C-13-001) of LMIS in male patients with prostate carcinoma on androgen deprivation therapy.
General Dosing instructions	Recommended dosage is leuprolide 42 mg every 6 months via subcuteaneous (SC) injection.
Dosing in patient subgroups (intrinsic factors)	• No dose adjustment is recommended based on age, race, or body weight. • The impact of hepatic or renal impairment on PK of leuprolide has not been evaluated.
Drug-drug interactions	• No drug interaction study is conducted. Leuprolide is a peptide and is not expected to have drug interactions with major CYP450 isoforms.
QTc Assessment	• No QTc assessment is conducted.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data / The Applicant's Position:
Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). The Sponsor established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from LMIS 50 mg (Study FSEE-CSC-100) and intends to rely on the clinical and non-clinical safety of Lupron®.

Camcevi™ 42 mg was designed to solve the apparent stability problem of leuprolide acetate forms, which require to be supplied separately and mixed immediately prior to administration. Camcevi™ 42 mg is a pre-mixed product, containing leuprolide mesylate equivalent of 42 mg leuprolide, formulated in a solution containing the excipients NMP and PLA. The difference in leuprolide salt weight has been accounted for so that the free base equivalent is the same between Camcevi™ 42 mg and comparable leuprolide 6-month depot forms such as Eligard® 45 mg.
Camcevi™ 42 mg is formulated to control and sustain the release of bioactive leuprolide (base) over a 6 month period after a single subcutaneous injection.

With more than 30 years in clinical use and many leuprolide acetate products approved and marketed, the clinical pharmacology of leuprolide is considered appropriately characterised, allowing an abridged development of Camcevi™ 42 mg with reliance on leuprolide acetate forms. Camcevi™ 42 mg contains the same active moiety as leuprolide acetate forms, distribution, metabolism, and excretion can be expected to be essentially the same once absorbed. Non-clinical studies with Camcevi™ 42 mg demonstrated similar biological activity, PD and PK profiles.

The PD and PK of subcutaneous leuprolide from Camcevi™ 42 mg (determined by serum leuprolide, serum testosterone, and serum luteinising hormone (LH) levels) was investigated in the main non-comparative clinical Study FP01C-13-001, comprising an additional, separate PK report (Study FSEE-CSC-101). Part I of Study FP01C-13-001 was conducted with the first 33 subjects, and the remainder of the subjects were entered into Part II after safety in Part I was established. In total, 137 patients were enrolled in the study. The PK population included all subjects who received at least 1 dose of Camcevi™ 42 mg, had at least one evaluable PK parameter, and were not excluded from analysis due to protocol deviations or other study related events that may impact the calculation or interpretation of the pharmacokinetic

variables. Therefore, 31 and 29 subjects were included in the PK analysis of the first and second dosing period in Part I, respectively. In Part II, 94 and 97 subjected were included, respectively (refer to NDA Module 2.7.2, Section 2.7.2.2).

For PK and PD assessments, blood samples were analysed for serum leuprolide, testosterone, and LH concentrations. Serum leuprolide levels were determined by means of a validated liquid chromatography-tandem mass spectrometric (LC-MS/MS) assay, with a quantitation range of 0.1 to 200 ng/mL. Serum testosterone levels were determined by means of a validated LC-MS/MS assay with a quantitation range of 0.05 to 10 ng/mL. For determination of serum LH levels, a validated ultra-sensitive chemiluminescense enzyme linked immunosorbent assay (ELISA) method was implemented, which had a quantitation range of 0.05 to 250.0 IU/L (refer to NDA Module 2.7.1, Section 2.7.1.1.2). Determination of serum PSA (prostate-specific antigen) levels were conducted by a central laboratory using commercial assays as part of a routine clinical diagnosis panel.

In addition to the main non-comparative clinical Study FP01C-13-001, the 'in-silico' PK bridging Study FSEE-CSC-100 between Camcevi™ 42 mg and the first leuprorlide acetate 1 mg form for daily administration (Lupron® 1 mg) was carried out (refer to NDA Module 2.7.1, Section 2.7.1.2.2).

A post-hoc evaluation of the potential impact of race / ethnic origin, age, and body weight on serum leuprolide PK and on serum testosterone suppression following Camcevi™ 42 mg was also carried out (PK Report FSEE-CSC-101; refer to NDA Module 2.7.2, Section 2.7.2.2.3.2).

Additional clinical pharmacology information to support the approval of Camcevi™ 42 mg is taken from the approved labeling of the Listed Drug, Lupron® Injection 1 mg (NDA 019010; AbbVie Inc, 2018) (refer to NDA Module 2.7.2, Sections 2.7.2.2.3, 2.7.2.2.3.1, 2.7.2.2.3.2).

Pharmacodynamics

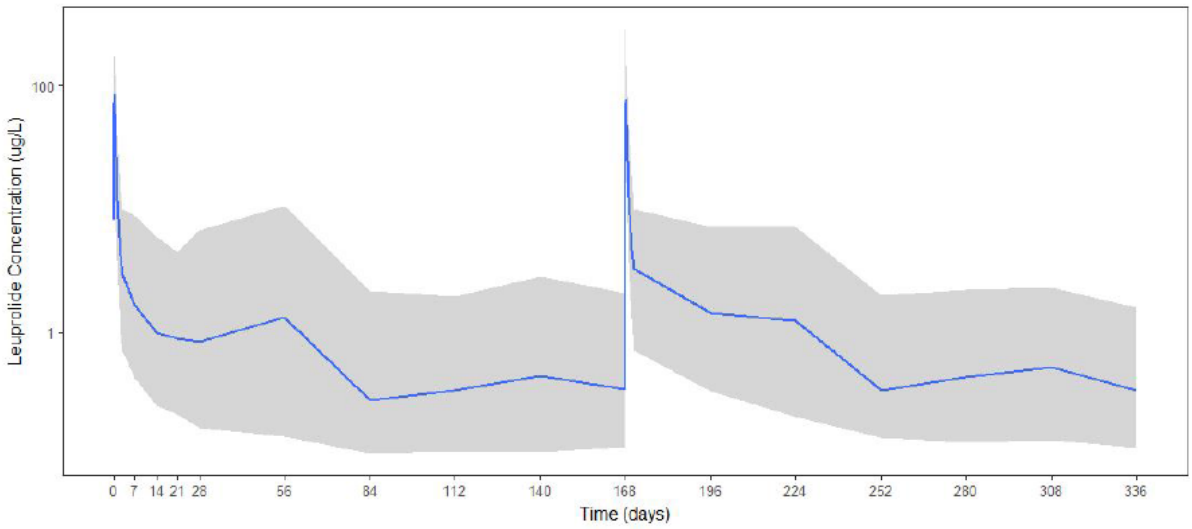
The PD of leuprolide with Camcevi™ 42 mg was primarily examined by its effect on serum testosterone levels (refer to NDA Module 2.7.2, Section 2.7.2.2), and suppression of serum testosterone served as key efficacy endpoint in the main clinical Study FP01C-13-001. Serum LH levels were also determined (refer to NDA Module 2.7.3).

As to be expected for a GnRH agonist, mean serum testosterone concentrations increased following the initial Camcevi™ 42 mg subcutaneous injection from a mean baseline value of 380 ng/dL and 492 ng/dL to peaks of 562 ng/mL and 739 ng/dL on Day 2 of Part I and II of Study FP01C-13-001, respectively (refer to NDA Module 2.7.2, Section 2.7.2.2.1).
From peak levels, serum testosterone levels fell rapidly after Day 7 to below 50 ng/dL (the pre-

defined castrate threshold) by Day 21 after the first dose (mean concentration on Day 21: 43.5 ng/dL for Part I and 38.2 ng/dL for Part II) (refer to NDA Module 2.7.2, Section 2.7.2.2.1). By Day 28, mean testosterone levels dropped below 20 ng/dL, and continued decreasing to mean concentrations of 6.02 ng/dL (Part I) and 9.87 ng/dL (Part II) by Day 168 prior to the second dose of Camcevi™ 42 mg. Following the second dose (Day 168), serum testosterone levels increased only slightly, and the levels were maintained below the castrate threshold (≤ 50 ng/mL) through the end of the study (Day 336) (refer to NDA Module 2.7.2, Section 2.7.2.2.1).
Similar effects of leuprolide exposure on serum testosterone levels were observed in subjects in Part II and in Part I of Study FP01C-13-001. An acute increase of serum testosterone levels was associated with rapid increases in serum leuprolide concentrations (refer to NDA Module 2.7.2, Sections 2.7.2.2.1, 2.7.2.2.2), which is congruent with clinical experience gained with leuprolide acetate forms (e.g., Hoda et al., 2017).

Pharmacokinetics
The PK profile of Camcevi™ 42 mg as determined in main Study FP01C-13-001 exhibited two phases: after dosing, an initial rapid increase of serum leuprolide concentration was observed, followed by a rapid decline over the first 3 days post-dose. After an initial burst phase characterised by mean high serum concentrations (> 90 ng/mL), mean serum leuprolide levels maintained relatively constant over each 24-week dosing interval. Leuprolide appeared to be released continuously by the third day after dosing with steady serum concentrations ("plateau" phase) through the 24 week dosing interval (mean concentration: 0.370 to 2.97 ng/mL). The mean serum leuprolide maximum concentration (C_{max}) was 94 to 100 ng/mL and it was reached after approximately 2 to 4 hours after the first and second dose of Camcevi™ 42 mg. The mean concentration of leuprolide then declined to around 0.4 to 0.5 ng/mL (C_{mon6}) at 24 weeks. Serum leuprolide concentrations and the associated PK following the first and second doses of Camcevi™ 42 mg were similar, suggesting lack of significant accumulation with repeated dosing at 24-week intervals (refer to NDA Module 2.7.1, Section 2.7.1.2.2; NDA Module 2.7.2, Section 2.7.2.2.3; PK Report FSEE-CSC-101; see also Applicant - Figure 2, Applicant – Figure 3).
Leuprolide displayed flip flop kinetics with multiple concentration peaks observed during the sustained release period. After the burst phase, a concentration peak was typically observed in both periods 56 days following administration of Camcevi™ 42 mg (Applicant - Figure 1).

Applicant - Figure 1: Median Serum Leuprolide Concentration vs Time After a Single Subcutaneous Dose of LMIS 50 mg (Period I, Day 0) or Multiple Dose (Period II, Day 168)

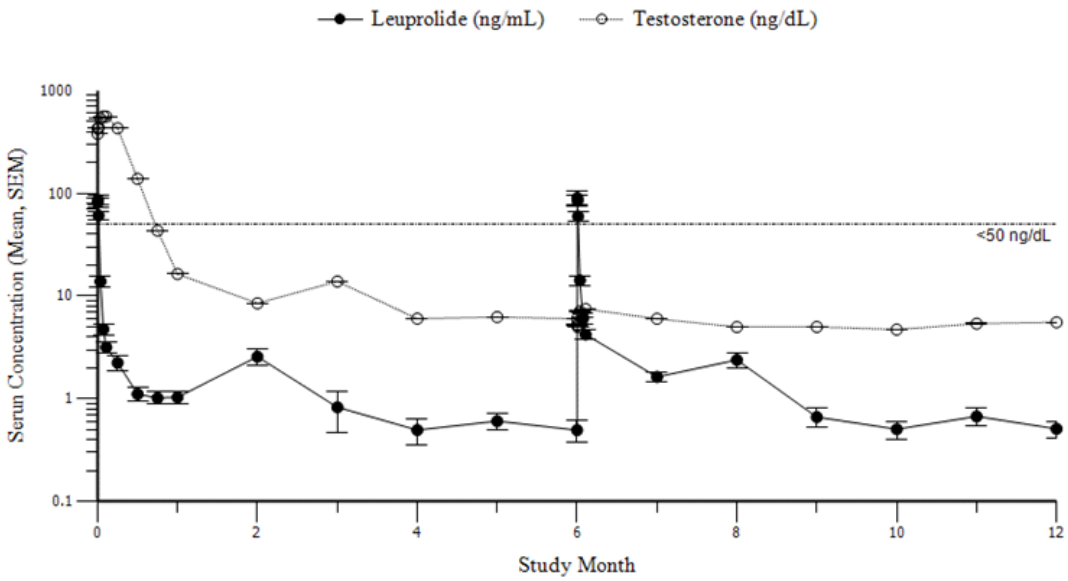


Gray areas indicate the 95% prediction interval around the median. The data are plotted on a semi log scale.
Source: PK Report FSEE-CSC- 101, Figure 5.2.1

Pharmacokinetic / Pharmacodynamic Relationship

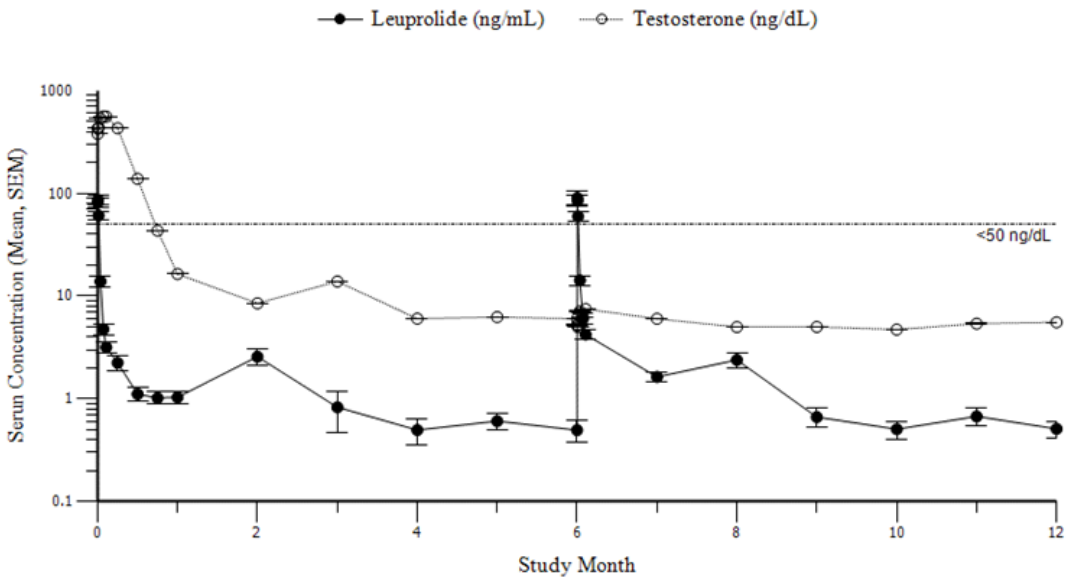
The response relationship of serum leuprolide and testosterone levels is depicted in Applicant - Figure 2 for Part I and Applicant – Figure 3 for Part II of Study FP01C-13-001.

Applicant - Figure 2: Arithmetic Mean Leuprolide and Testosterone Serum Concentration-time After LMIS 50 mg Subcutaneous Injections in Part I of Study FP01C-13-001



Source: Study FP01C-13-001, Figure 11 11

Applicant – Figure 3: Arithmetic Mean Leuprolide and Testosterone Serum Concentration-time After LMIS 50 mg Subcutaneous Injections in Part II of Study FP01C-13-001



Source: Study FP01C-13-001, Figure 11 12

The transient serum testosterone level increase was associated with the burst phase of serum leuprolide concentrations following the first dose of Camcevi™ 42 mg. This effect, as for other GnRH agonists, may be attributed to the transient acute-on-chronic surge of LH levels raised by initial burst leuprolide serum level. Apart from the acute increase, serum testosterone levels were maintained below the castrate threshold (≤ 50 ng/dL) from Day 21 (after the first Camcevi™ 42 mg injection) through the end-of-study Day 336 (refer to NDA Module 2.7.2, Section 2.7.2.2.2).

By Day 28, the mean testosterone serum level was even below 20 ng/dL (mean: 16.4 ng/dL), decreased continuously and reached the mean concentration of 6.02 ng/dL by Day 168 prior to the second administration of Camcevi™ 42 mg. With the second dose of Camcevi™ 42 mg, testosterone serum levels increased slightly, reaching a maximum on Day 224 (56 days post second injection), with a mean testosterone serum level of 11 ng/dL. Even with increased serum exposure of leuprolide due to the second Camcevi™ 42 mg subcutaneous injection, the mean testosterone serum level was maintained below the pre-defined castration threshold, with a mean concentration of 5.56 ng/dL on Day 336 (Study FP01C-13-001).

Even if the more conservative castrate threshold of ≤ 20 ng/mL is considered, proposed on the basis of androgen deprivation observed with bilateral orchiectomy, Camcevi™ 42 mg proved to

effectively suppress serum testosterone (Study FP01C-13-001).

Comparison of Camcevi™ 42 mg *versus Listed Drug Leuprolide Acetate 1 mg (Lupron®)*
Foresee conducted an in-silico comparison of the steady-state PK parameters of Camcevi™ 42 mg and leuprolide 1 mg for daily injection (Lupron® 1 mg) (Study FSEE-CSC-100; refer to NDA Module 2.7.2, Section 2.7.1.2.2). The PK modelling and simulation study compared Camcevi™ 42 mg PK data from study FP01C-13-001 (Part 1, PK/PD Phase I) and published Lupron® 1 mg PK data (Sennello et al., 1986). Single-dose leuprolide 1 mg PK data was used to generate a simulated 6-month, population PK time-course for steady-state comparison with Camcevi™ 42 mg.
The outcome supports bridging to safety data obtained for the initially approved leuprolide 1 mg form requiring daily administration (Lupron® 1 mg) as it shows that the overall exposure to leuprolide with Camcevi™ 42 mg lies well within the therapeutic range (0.2 to 2.0 ng/mL) and does not exceed the range of exposure considered safe.

Impact of Race / Ethnic Origin, Age, and Body Weight on Serum Leuprolide Pharmacokinetics and Serum Testosterone Suppression
In the PK Report FSEE-CSC-101, the Applicant assessed the potential impact of race, body weight, and age at the time of injection on serum leuprolide PK (refer also to NDA Module 2.7.2, Section 2.7.2.2.3.2).

Ethnic origin / race: Similar serum leuprolide median profiles were observed over the 2 dosing periods with subcutaneous Camcevi™ 42 mg for White, Asian, Black, or other races. No significant differences were observed. Median serum testosterone concentration versus nominal time profiles were similar among races (refer to NDA Module 2.7.2, Section 2.7.2.2.3.2; PK Report FSEE-CSC-101).

Age: Serum leuprolide peak levels as well as overall exposure were higher in subjects aged > 79 years compared to subjects aged < 60 years. Median serum testosterone concentration-time profiles were comparable among age categories (< 60, 60-69, 70-79 or > 79 years old) (refer to NDA Module 2.7.2, Section 2.7.2.2.3.2; PK Report FSEE-CSC-101).

Body weight: Subjects > 100 kg body weight showed decreased serum leuprolide peak levels and overall exposure as compared to subjects < 40 kg. Median serum testosterone concentration-time profiles were comparable among body weight categories (< 75, 75-84, 85-100 or > 100 kg body weight) (refer to NDA Module 2.7.2, Section 2.7.2.2.3.2; PK Report FSEE-CSC-101).

The FDA's Assessment:

The FDA generally agrees with the Applicant's position that the clinical pharmacology program supports the use of Camcevi™ 42 mg for the treatment of adult patients with advanced prostate cancer. The PK-PD relationship, i.e., leuprolide and testosterone serum concentration-time, supports the dose selection of Camcevi™ as 42 mg SC injection once every 6 months. The post-hoc analysis of impact of age, race, and body weight on PK and PD was characterized. The bioanalytical methods for leuprolide and terstosteron measurements are validated according to applicable guidances and fulfilled requirements with respects to linearity, selectivity, accuracy, and precision.

The clinical pharmacology program for the current NDA includes the following studies:

- **Study FP01C-13-001**: An open-label, single-arm study to evaluate the safety, efficacy, and PK of LMIS 50 mg in patients with advanced prostate cancer
- **Study FSEE-CSC-101**: a PK report of leuprolide to assess the PK of SC administration of LMIS 50 mg and the potential impact of period, age, body weight, race, and lot formulation on leuprolide PK
- **Study FSEE-CSC-100**: a modeling and simulation approach to compare the levels of leuprolide following a repeated LMIS 50 mg dose in Study FP01C-13-001 to steady state levels of leuprolide following repeated 1 mg IV injection of Lupron

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

In accordance with other approved leuprolide depot forms suitable for 6-monthly administration in the palliative treatment of prostate cancer, Camcevi™ 42 mg is proposed to be dosed subcutaneously in 6-month intervals (42 mg leuprolide base every 6 months) (refer to NDA Module 2.5, Section 2.5.1).

The dosage strength of Camcevi™ 42 mg is equivalent to comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), each containing 42 mg of leuprolide base, and the proposed dosing schedule for Camcevi™ 42 mg (42 mg leuprolide base every 6 months per subcutaneous injection) corresponds with approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg) (refer to NDA Module 2.5, Section 2.5.1).

The FDA's Assessment:

The FDA agrees with the Applicant that the proposed dosing regimen of Camcevi™ 42 mg, i.e, 42 mg leuprolide base every 6 months per SC injection, is supported by the PK and PD relationship, and comparability to other approved leuprolide acetate depot forms:

1) As the Applicant presented in Section 6.2.1, following the first and the second doses of CAMCEVI, mean serum leuprolide concentrations rose rapidly to reach the C_{max} of 94.5 and 99.0 ng/mL at 3.23 and 2.08 hours, respectively, and declined to maintain a low level as 0.497–2.57 (after Day 3 to Day 168) and 0.507–2.39 ng/ml (after Day 171 to Day 336). The mean serum testosterone concentrations transiently increased following the first dose of CAMCEVI, then fell to below castrate threshold levels (≤ 50 ng/dL) within 3 weeks of the first dose and remain below the threshold. (Applicant Figure 2 and Figure 3). This PK-PD time-concentration relationship revealed the rapid effect of leuprolide on reducing serum testosterone levels, supporting the use of leuprolide 42 mg with a dosing frequency as once every 6 months.
2) The FDA agrees that the dosage strength of Camcevi™ 42 mg is comparable to Eligard® 45 mg. Both drugs are administered via SC injection once 6 months. In addition, the PK-PD relationship is similar for Eligard® 45 mg as that for Camcevi™ 42 mg.

Based on the above, the FDA agrees that the Applicant proposed dosing regimen of Camcevi™ 42 mg is established.

6.2.2.2 Therapeutic Individualization

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with reliance of Camcevi™ 42 mg according to approved leuprolide predecessors.

In accordance with other approved leuprolide depot forms suitable for 6-monthly administration in the palliative treatment of prostate cancer, Camcevi™ 42 mg is proposed to be dosed subcutaneously in 6-month intervals (42 mg leuprolide base every 6 months) (refer to NDA Module 2.5, Section 2.5.1).

The dosage strength of Camcevi™ 42 mg is equivalent to comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), each containing 42 mg of leuprolide base, and the proposed dosing schedule for Camcevi™ 42 mg (42 mg leuprolide base every 6 months per subcutaneous injection) corresponds with approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg) (refer to NDA Module 2.5, Section 2.5.1).

The proposed dosing schedule for Camcevi™ 42 mg follows the dosing recommendations of comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), with no therapeutic individualization foreseen in the product labeling.

The FDA's Assessment:

The FDA agrees with the Applicant that no theraperutic individualization is necessary for Camcevi™ 42 mg. As the Applicant presented in Section 6.2.1, a post-hoc evaluation of the potential impact of race / ethnic origin, age, and body weight on serum leuprolide PK and on serum testosterone suppression following Camcevi™ 42 mg was carried out in the PK Report FSEE-CSC-101, based on the Study FP01C-13-001 PK population:

- Age: Leuprolide exposure increases when age increase (51 to 88 years). Leuprolide exposure over 6 months was higher by 2-fold in patients > 79 Y compared to subjects < 60 Y. Serum testosterone levels are similar between age categories.
- Body weight: Leuprolide exposure decreases when body weight decreased (54 to 134 kg). Leuprolide exposure over 6 months was decreased by 20% in subjects > 100 kg compared to subjects < 75 kg. Serum testosterone levels are similar between age categories.
- Race: Similar serum leuprolide profiles were observed over the 2 dosing periods for White, Asian, Black, or Other races. Serum testosterone levels are similar between age categories.

Based on the above, it is noted that race does not affect leuprolide or testosterone serum

levels. Although the leuprolide exposure may change with age or body weight, it does not affect the serume testosterone levels. Therefore, the impact of age, body weight, and race is not clinically relevant. No dose adjustment is needed for Camcevi™ 42 mg with regard to these intrinsic factors. See Appendix 19.4.2 for details.

6.2.2.3 Outstanding Issues

Data / The Applicant's Position:
None.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data / The Applicant's Position:
Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). The Sponsor established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from Camcevi™ 42 mg (Study FSEE CSC 100) and intends to rely on the clinical and non-clinical safety of Lupron®.
With more than 30 years in clinical use and many leuprolide acetate products approved and marketed, the clinical pharmacology of leuprolide is considered appropriately characterised, allowing an abridged development of Camcevi™ 42 mg with reliance on leuprolide acetate forms.

Biopharmaceutical Aspects
Camcevi™ 42 mg is formulated to control and sustain the release of bioactive leuprolide (base) over a 6 month period after a single subcutaneous injection. Camcevi™ 42 mg is a pre-mixed product, containing leuprolide mesylate equivalent of 42 mg leuprolide, formulated in a solution containing the excipients NMP and PLA (Applicant - Table 1).
The drug delivery system consists of a biodegradable material dissolved in a biocompatible solvent and the bioactive agent that is modified to achieve optimal formulation stability and release profile. The enhanced stability allows the Camcevi™ 42 mg formulation to be pre-filled into a ready-to-use syringe with a suitable storage shelf-life (refer to NDA Module 2.3).

Applicant - Table 1: Composition of LMIS 50 mg Pre-Filled Syringe

Ingredient	%wt/wt	Amount delivered per syringe (mg)	Function	IID Maximum Potency[a]
Leuprolide mesylate	(b) (4)	48 (b) (4)	API	(b) (4)
(b) (4) (PLA; polylactide)		(b) (4)	Biodegradable polymer, (b) (4)	
(b) (4) (N-methyl-2-pyrrolidone, or NMP)		136 (b) (4)	Solvent	
Total delivered weight	100.00	(b) (4)		

API = active pharmaceutical ingredient; IID = FDA Inactive Ingredients Database; n/a = not applicable
[a] For subcutaneous route of administration.
Source: NDA Module 2.5, Section 2.5.2

As Camcevi™ 42 mg has not undergone changes in the formulation during the clinical development, no formal comparative bioavailability / bioequivalence studies between Camcevi™ 42 mg formulations are required and have not been conducted.

Due to the proposed route of administration (subcutaneous injection), no studies on the effect of food on Camcevi™ 42 mg are required and have not been conducted.

For bioanalytical methods, refer to Section 6.2.1 above.

Pharmacodynamics

Leuprolide acts as an agonist at pituitary GnRH receptors. By interrupting the normal pulsatile stimulation of, and thus desensitising, the GnRH receptors, it indirectly downregulates the secretion of LH, leading to hypogonadism and thus a marked reduction in serum testosterone levels when given continuously to males (GnRH analogues; ATC code: L02A E02). This effect is reversible upon discontinuation. Administration of leuprolide results in an initial increase in circulating levels of LH, leading to a transient increase in levels of the gonadal steroids testosterone and dihydrotestosterone in males. Continuous availability of leuprolide results in decreased levels of LH and sustained testosterone suppression (Hoda et al., 2017; Sethi and Sanfilippo, 2009; refer to NDA Module 2.5, Section 2.5.1).
With more than 30 years in clinical use and many leuprolide acetate products approved and marketed, the clinical pharmacology of leuprolide is considered appropriately characterised (Hoda et al., 2017; Periti et al., 2002; Sethi and Sanfilippo, 2009; refer to NDA Module 2.5, Section 2.5.1).

Pharmacokinetics

Absorption of and exposure to leuprolide following subcutaneous administration of Camcevi™ 42 mg was investgated in the main Study FP01C-13-001 (refer also to PK Report FP01C-13-001). Because Camcevi™ 42 mg contains the same active moiety as leuprolide

acetate forms, the distribution, metabolism, and excretion can be expected to be the same once absorbed.

Absorption, Exposure
The PK profile of Camcevi™ 42 mg as determined in main Study FP01C-13-001 exhibited two phases: after dosing, an initial rapid increase of serum leuprolide concentration was observed, followed by a rapid decline over the first 3 days post-dose. After an initial burst phase characterised by mean high serum concentrations (> 90 ng/mL), mean serum leuprolide levels maintained relatively constant over each 24-week dosing interval. Leuprolide appeared to be released continuously by the third day after dosing with steady serum concentrations ("plateau" phase) through the 24-week dosing interval (mean concentration: 0.370 to 2.97 ng/mL). Serum leuprolide concentrations and the associated PK following the first and second doses of Camcevi™ 42 mg were similar, suggesting lack of significant accumulation with repeated dosing at 24-week intervals (refer to NDA Module 2.7.1, Section 2.7.1.2.2; NDA Module 2.7.2, Section 2.7.2.2.3; PK Report FSEE-CSC-101).

Distribution
The distribution of leuprolide after subcutaneous administration of Camcevi™ 42 mg has not been specifically investigated. Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). Reference is made to the LD (refer to NDA Module 2.7.2, Section 2.7.2.2.3).

Metabolism
No dedicated clinical study on the metabolism of leuprolide with administration of Camcevi™ 42 mg has been conducted. Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). Reference is made to the LD (refer to NDA Module 2.7.2, Section 2.7.2.2.3).

Elimination, Excretion
Elimination and excretion of leuprolide following subcutaneous administration of Camcevi™ 42 mg have not been specifically investigated, and no drug excretion study was conducted with leuprolide. Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). Reference is made to the LD (refer to NDA Module 2.7.2, Section 2.7.2.2.3).

Special Populations
Renal impairment: The PK of leuprolide following Camcevi™ 42 mg in renally impaired subjects has not been determined. Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.).

Reference is made to the listed drug (refer to NDA Module 2.7.2, Section 2.7.2.2.3).

Hepatic impairment: The PK characteristics of leuprolide following Camcevi™ 42 mg in subjects with hepatic impairment has not been investigated. Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). Reference is made to the listed drug (refer to NDA Module 2.7.2, Section 2.7.2.2.3).

Pediatrics: No investigations have been conducted with Camcevi™ 42 mg in pediatric populations. As drug intended for use in prostate cancer, Camcevi™ 42 mg is not indicated for use in children.

Elderly: In the clinical trials on leuprolide, the majority of subjects studied were of higher age (including the Applicant's main clinical Study FP01C-13-001; refer also to NDA Module 2.7.2, Section 2.7.2.2.3.2), which is to be expected in prostate cancer.

Gender: No investigations have been conducted with Camcevi™ 42 mg in women. As a drug intended for use in prostatic cancer, Camcevi™ 42 mg is not indicated for use in women.

For race / ethnic origin, age, and body weight, refer to Section 6.2.1 above.

Drug Interactions
No specific drug-drug interaction studies have been carried out on leuprolide following administration of Camcevi™ 42 mg. Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as reference (NDA 019010; AbbVie, Inc.). Reference is made to the LD (refer to NDA Module 2.7.2, Section 2.7.2.2.3.1).

The FDA's Assessment:
The FDA agrees with the Applicant's position that the scientific bridge is generally established to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from Camcevi™ 42 mg.
Based on population PK Study FSEE-CSC-100, the exposure to leuprolide at steady state is approximately 5 times higher from Lupron than from LMIS, the overall exposure ($AUC_{0\text{-}6mon}$) of leuprolide is also significantly lower for LMIS 50 mg, as well as the absolute C_{max}. (Table 1). Given the low AUC and C_{max} at steady state of LMIS revealed an adequate safety margin of LMIS for a long term use, the FDA agrees that the scientific bridge is established that Camcevi™ 42 mg could rely on the nonclinical and clinical safety profile of Lupron® from a long term perspective.
However, it is also noted that the LMIS 50 mg would have ~7-fold high $AUC_{0\text{-}24h}$ as compared to

Lupron 1 mg due to the higher dose of LMIS 50 mg on Day 1, the safety of LMIS after single dose for short term would still be replied on the results from Study FP01C-13-001.

Table 2. Leuprolide exposure (geometric mean (%CV)) at steady stated following Lupron Injection 1 mg QD dose and LMIS 50 mg (i.e., Camcevi™ 42 mg) once every 6 month dose.

Treatment	AUC_{0-24h} (ng.h/mL)	AUC_{0-6mo} (ng.h/mL)	C_{max} (ng/mL)	C_{ss}[b] (ng/mL)	Swing $(C_{max}-C_{min})/C_{min}$	Leuprolide Doses (mg)
Lupron 1 mg	147 (14.8)	24696 (14.8)[a]	116 (33.6)	6.11 (14.8)	1932	168
LMIS 50 mg	975 (64.1)	6611 (36.9)	79.5 (74.0)	1.30 (38.2)	180[c]	45

[a] Extrapolated from AUC_{0-24h} using the formula: $AUC_{0-24h} \times 168$ days
[b] C_{ss} Lupron = $AUC_{0-24h}/24$; C_{ss} LMIS 50 mg = $AUC_{(\text{after burst phase, set to } 72-4032\text{ h})}/(4032-72)$
[c] Includes burst phase

Source: CSR FSEE-CSC-100 Table 4.3.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway, with Lupron® Injection 1 mg as LD (NDA 019010; AbbVie, Inc.).

According to the aim of ADT in prostate cancer, suppression of serum testosterone levels below castrate threshold, Camcevi™ 42 mg was primarily examined by its effect on serum testosterone levels (refer to NDA Module 2.7.2, Section 2.7.2.2), and suppression of serum testosterone served as key efficacy endpoint in the main clinical Study FP01C-13-001. Serum LH levels were also determined (refer to NDA Module 2.7.3).
Following Camcevi™ 42 mg administration in 6-month intervals, serum testosterone levels were maintained below the castrate threshold (≤ 50 ng/dL). Even if the more conservative castrate threshold of ≤ 20 ng/mL is considered, proposed on the basis of androgen deprivation observed with bilateral orchiectomy, Camcevi™ 42 mg proved to effectively suppress serum testosterone (Study FP01C-13-001).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

In accordance with other approved leuprolide depot forms suitable for 6-monthly administration in the palliative treatment of prostate cancer, Camcevi™ 42 mg is proposed to be dosed subcutaneously in 6-month intervals (42 mg leuprolide base every 6 months) (refer to NDA Module 2.5, Section 2.5.1).

The dosage strength of Camcevi™ 42 mg is equivalent to comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), each containing 42 mg of leuprolide base, and the proposed dosing schedule for Camcevi™ 42 mg (42 mg leuprolide base every 6 months per subcutaneous injection) corresponds with approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg) (refer to NDA Module 2.5, Section 2.5.1).

Based on the study population of the main Study FP01C-13-001, being cross-reginal and multicentre, deemed representative for the general patient population and resembling the study patient population of main registration trials for approved leuprolide depot forms (e.g., Crawford et al., 2006 [Eligard® 45 mg]), the proposed dosing regimen for Camcevi™ 42 mg is considered appropriate.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data / The Applicant's Position:
Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

In accordance with other approved leuprolide depot forms suitable for 6-monthly administration in the palliative treatment of prostate cancer, Camcevi™ 42 mg is proposed to be dosed subcutaneously in 6-month intervals (42 mg leuprolide base every 6 months) (refer to NDA Module 2.5, Section 2.5.1).

The dosage strength of Camcevi™ 42 mg is equivalent to comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), each containing 42 mg of leuprolide base, and the proposed dosing schedule for Camcevi™ 42 mg (42 mg leuprolide base every 6 months per subcutaneous injection) corresponds with approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg) (refer to NDA Module 2.5, Section 2.5.1).

The proposed dosing schedule for Camcevi™ 42 mg follows the dosing recommendations of comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), with no alternative dosing regimen or management strategy for subpopulations in the product labeling of approved leuprolide forms. Studies on Camcevi™ 42 mg revealed no indication for requiring further specific dosing recommendations.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data / The Applicant's Position:

Due to the proposed route of administration for Camcevi™ 42 mg (subcutaneous injection), as for approved leuprolide forms given parenterally, food-drug interactions are not to be expected.

No drug-drug interaction studies have been conducted with Camcevi™ 42 mg, and no such studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur (refer to NDA Module 2.7.2, Section 2.7.2.2.3.2).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data / The Applicant's Position:

Leuprolide (as an acetate salt) has been approved for the palliative treatment of prostate cancer in the United States since 1985 (Lupron® Injection; NDA 019010; AbbVie, Inc.). For this NDA, Foresee Pharmaceuticals (Foresee, or the Sponsor) conducted one Phase 3 study (Study FP01C-13-001) with a safety extension (Study FP01C-13-001-EX) to evaluate the safety and efficacy of LMIS 50 mg (Camcevi™ 42 mg). The Sponsor established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from Camcevi™ 42 mg (Study FSEE-CSC-100) and intends to rely on the clinical and nonclinical safety of Lupron®.

The proposed LMIS product differs from currently approved leuprolide products in that the salt used for the proposed drug product (mesylate) differs from that used in the currently approved products (acetate). Camcevi™ 42 mg is a pre-mixed product containing 42 mg leuprolide (~48 mg of leuprolide mesylate) formulated in a solution of NMP and PLA. The difference in salt weight has been accounted for so that the free base equivalent is the same between the proposed Camcevi™ 42 mg product and the currently approved 45 mg leuprolide acetate products. The proposed product is formulated to control and sustain the release of the bioactive leuprolide over a 6-month period after a single subcutaneous administration. Unlike currently marketed leuprolide products that require reconstitution and/or mixing prior to administration, Camcevi™ 42 mg is a combination product that will be supplied ready-to-use in a single sterile, pre-filled syringe (refer to NDA Module 3.2.R.1.P.3).

Foresee Pharmaceuticals has conducted a single pivotal clinical Phase 3, uncontrolled, mulicentre, open-label, single-arm, 12-month, two-part PK, safety and PD / efficacy study in patients with advanced prostate cancer in need of ADT (Study FP01C-13-001), followed by a 12-month safety extension (Study FP01C-13-001-EX) (Applicant - Table 2). Apart from the USA and Taiwan, the main clinical Study FP01C-13-001 has been conducted in Austria, Germany, Czech Republic, Slovakia, Lithuania, and Poland. The safety extension Study FP01C-13-001-EX has been conducted in the USA only (Applicant - Table 2).

Applicant - Table 3: Overview of Clinical Studies of LMIS 50 mg (Camcevi™ 42 mg)

Study No. (Country)	Study Objectives	Design / Duration	Study Treatment	Study Subjects	Study Status
FP01C-13-001 Phase 3 (USA; Austria, Germany, Czech Republic, Slovakia, Lithuania, Poland, Taiwan)	Safety / tolerability, Efficacy; PK / PD profile; Serum testosterone, LH, and PSA levels	Uncontrolled, multicenter, open-label, single-arm; 12 months	LMIS 50 mg every 6 months; subcutaneous injection	Enrolled: n=137 Completed: n=133 Males with histologically confirmed prostate carcinoma; subjects judged to be candidate for androgen ablation therapy	Completed
FP01C-13-001-EX Phase 3 (USA)	Safety / tolerability; Extension of Study FP01C-13-001	Uncontrolled, multicenter, open-label, single-arm; 12 months	LMIS 50 mg every 6 months; subcutaneous injection	Enrolled: n=30 Prostate carcinoma subjects successfully completing Study FP01C-13-001	Completed

LH = luteinising hormone; LMIS = leuprolide mesylate injectable suspension; PD = pharmacodynamics; PK = pharmacokinetics; PSA = prostate-specific antigen.
Source: Study FP01C-13-001, Study FP01C-13-001-EX

The safety extension Study FP01C-13-001-EX was focused on further characterising Camcevi™ 42 mg safety over a prolonged period. Therefore, the safety extension Study FP01C-13-001-EX is not further summarized in the following sections on efficacy.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. This NDA is supported by one single arm, open-label clinical trial (FP01C-13-001) in which leuprolide injectable emulsion was administered to 137 patients on Days 0 and 168, and serum testosterone levels were measured at regular intervals from Day 28 through Day 336. The extention phase (FP01C-13-001-EX) collected additional safety data on 30 patients who continued treatment after Day 336.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study FP01C-13-001

Trial Title

An open-label, single-arm study of the safety, efficacy, and pharmacokinetic behaviour of leuprolide mesylate injectable suspension (LMIS 50 mg) in subjects with advanced prostate carcinoma)

Trial Design

The Applicant's Description:

The main Study FP01C-13-001 was a multicenter, open-label, single-arm study conducted in 137 males with prostate carcinoma in need for androgen deprivation therapy (male adult subjects with histologically confirmed prostate carcinoma, baseline morning serum testosterone level > 150 ng/dL, Eastern Cooperative Oncology Group (ECOG) performance ≤ 2).

Subjects were scheduled to receive 2 doses of Camcevi™ 42 mg, administered 6 months apart, in an unblinded fashion.

This study was conducted in two parts. Part I included the first 33 subjects, who had more frequent monitoring for safety. Once ≥ 90% of the 33 subjects achieved suppression of serum testosterone concentrations to castration levels (≤ 50 ng/dL) within 28 days of the initial dose, with acceptable safety and tolerability, Part II was opened, and the remainder of the subjects was enrolled (refer to NDA Module 2.5.5.).

The FDA's Assessment:
The FDA agrees with the Applicant's description of the trial design. FP01C-13-001 was conducted in men with hormone-sensitive prostate cancer, a patient population for whom androgen deprivation therapy is indicated. The Applicant's statement above that the first 33 subjects had "more frequent monitoring for safety" refers to the fact that the first 10 patients enrolled underwent additional interim safety reviews conducted by an Independent Data Monitoring Committee at the end of Weeks 2, 4, 12, and 24.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was suppression of serum testosterone levels below castrate levels (≤ 50 ng/dL), an accepted surrogate endpoint for GnRH agonists in ADT.

Secondary endpoints included post-suppression elevation of serum testosterone (> 50 ng/dL), serum PSA levels, and serum LH levels.

PSA and LH provide additional assessments of efficacy, as PSA is a marker for prostate cancer and LH production is upstream of testosterone (for validated bioanalytical methods used for determination of serum testosterone and LH, refer to NDA Module 2.7.1, Section 2.7.1.1.2).

The FDA's Assessment:

The FDA agrees with the Applicant's description of the primary efficacy endpoint. The primary efficacy endpoint of FP01C-13-001 was serum testosterone ≤ 50 ng/dL achieved and maintained from Day 28 to Day 336 estimated by the Kaplan-Meier method. This primary efficacy endpoint is and its prespecified statistical analysis plan were consistent with the FDA draft guidance, Advanced Prostate Cancer: Developing GonadotropinReleasing Hormone Analogues Guidance for Industry (https://www.fda.gov/media/129027/download). Single-arm clinical trials demonstrating the achievement and maintenance of castrate testosterone levels have been the basis for the FDA approvals of other depot formulations of leuprolide.

The primary efficacy endpoint of Protocol FP01C-13-001 was changed from *less than* 50 ng/dL (i.e. < 50 ng/dL) in the original protocol submitted 15 April 2014 to *less than or equal* to 50 ng/dL (i.e. ≤ 50 ng/dL) with the first protocol amendment submitted June 9, 2014. The Applicant and the FDA calculated and reported the primary efficacy endpoint of FP01C-13-001 based on a cutoff of ≤ 50 ng/dL. One patient is affected by changing the cutoff from ≤ 50 ng/dL to < 50 ng/dL in NDA. The final conclusion is not changed, as the lower bound of the 95% CI with both cutoffs is > 90% (see section below titled Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) for further details).

Table 4 summarizes the censoring rules that the Statistical Analysis Plan pre-specified for the primary efficacy analysis to calculate the percentage of patients with serum testosterone ≤ 50 ng/dL at Day 28 and maintained through Day 336 based on the Kaplan-Meier method.

Table 4. Applicant's Censoring Rules in the Primary Analysis of Castration Rate Estimation

Suppression by Day 28 visit			To be handled as
Patient discontinued	Day 28-336 or Day of discontinuation		
	2+ missing testosterone values	Any escape	
Yes	No	No	Censored on day of last measurement

			prior to discontinuation
Yes	No	Yes	Event on day of first escape
Yes	Yes	No	Censored on day of last measurement before the first missing
Yes	Yes	Yes	Event on day of first escape
No	No	No	Censored on EOS visit
No	No	Yes	Event on day of first escape
No	Yes	No	Censored on day of last measurement before the first missing
No	Yes	Yes	Event on day of first escape
No suppression by Day 28*			Event on Day 28

*Including patients without suppression at day 28 visit or patients with missing testosterone value at day 28 were to be analyzed as event on day 28.
[Source: SAP Page 18]

Per the FDA's draft guidance on GnRH product development [*https://www.fda.gov/media/129027/download*], the FDA recommends the following rules for handling missing testosterone (T) assessments:

- Patients with one or more consecutive missing T levels and a non-castrate T level after the missing time point should be considered to have had a treatment failure at the first missing time point.
- Patients with castrate T levels immediately before and after a single missing T level should not be considered to have had a treatment failure at the missing time point.
- Patients with two or more consecutive missing T levels and castrate T levels immediately before and after the missing time points should be censored at their last T level before the missing data.

Per the above recommendations from the FDA's draft guidance, whether a patient with missing assessment(s) should be censored or considered as a failure would depend on the testosterone levels immediately before and after the missing assessment(s). The censoring rules handing missing assessments prespecified in the study analysis plan do not consider the timing of castration failure.

The review team evaluated the observed testosterone data to check whether missing data could cause discordant results per the censoring rules as specified in the SAP versus the FDA's draft guidance [see section below titled Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) for further details].

Statistical Analysis Plan and Amendments

<u>The Applicant's Description:</u>

The statistical analysis plan (SAP) of Study FP01C-13-001 for Camcevi™ 42 mg in prostate cancer patients (version 1.3; December 1, 2016) was prepared by QPS-Qualitix, with approval of the Sponsor. The SAP was based on the study protocol FP01C-13-001, Version 1.4 (October 14, 2015).

The efficacy analysis for primary endpoints was to determine the percentage of subjects with a serum testosterone concentration suppressed to castrate levels (≤ 50 ng/dL) by Day 28 ± 1 (day) following the first injection of Camcevi™ 42 mg and to determine the percentage of subjects with serum testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 (remaining duration of the study). The percentage of subjects with a serum testosterone of ≤ 50 ng/dL (castrate level) by Day 28 ± 1 (day) was analyzed using a standard large sample normal approximation to a Binomial distribution. The percentage of subjects with testosterone suppression (≤ 50 ng/dL) from Day 28 through Day 336 was analyzed using a Kaplan-Meier approach. In this analysis, an event was defined as the occurrence in a subject with a testosterone level > 50 ng/dL at or before Day 336.

For descriptive statistics, continuous variables were described using descriptive statistics: number of observations (n), mean, median, standard deviation (SD), minimum, maximum, Hodges–Lehmann estimator and 95% confidence intervals. In addition, the paired t test or Wilcoxon signed rank test was used to test the change from baseline for continuous variables. Frequencies and percentages were used for summarizing discrete (categorical) variables. The denominator for all percentages, unless otherwise specified, was the number of subjects in the specified population. Categorical variables were presented by frequency and percentage. The change from the baseline was tested by paired t-test.

If the data strongly indicated a violation of the normal assumption (the p-value of test of normality is <0.05), the Wilcoxon signed rank test was applied for analysis otherwise.

Unless otherwise specified, all statistical assessments were two-sided and evaluated at significance level of 0.05.

The baseline value was defined as the last value collected prior to the start of first dose of study drug administration unless otherwise specified. Nominal visit was used for the analyses of efficacy and safety endpoints.

Six interim analyses (5 interim analyses of safety and 1 interim analysis of efficacy) were conducted during this study, overseen by an Independent Data Monitoring Committee and an Independent Statistical Center. The objective of the safety interim analyses was to assess the feasibility of continuing with LMIS 50 mg after assessment of safety in 33 subjects in Part I of Study FP01C-13-001. Safety interim analyses 1 to 4 were conducted for the first 10 subjects at the end of Week 2, Week 4 (approximately 1 month), Week 12 (approximately 3 months), and

Week 24 (approximately 6 months). Safety interim analysis 5 was conducted for the first 33 subjects after Day 28. The objective of the efficacy interim analysis was to assess whether the number of enrolled subjects was appropriately powered based on observed dropout rate and the castration rate at Day 28. Efficacy interim analysis was conducted when 100 subjects completed the Day 28 assessment. The additional sample sizes were inflated to allow for a 10% dropout. The IDMC Charter provided guidance and detail information for the stopping rules (Study FP01C-13-001, Section 9.7.1).

Assuming no increase in the sample size following the sample size re-estimation, a maximum of 133 subjects was anticipated to be enrolled in this study. A sample size of 120 was estimated to achieve the 85% power to detect a difference (P1-P0) of 0.0700 using a one-sided binomial test. The target significance level was 0.0250. This assumed that the population proportion under the null hypothesis was <0.90 and under the alternative to be 0.97. The drop-out rate was expected to be 10% (approximately 13 subjects) in the study before Day 336. A total of 137 subjects were enrolled in the study at the end (Study FP01C-13-001, Section 9.7.2).

No changes were made in the conduct of the study or planned analyses. This study was performed in accordance of the study protocol FP01C-13-001, Version 1.4 (October 14, 2015) (Study FP01C-13-001, Section 9.8).

The FDA's Assessment:
The FDA agrees with the Applicant's description of the statistical analysis plan. The Statistical Analysis Plan specified that the study would be considered as achieving a positive efficacy outcome if the lower 95% confidence interval bound for the Kaplan-Meier estimate of the proportion of patients who received at least one dose of leuprolide injectable emulsion and achieved and maintained castration levels from Day 28 through Day 336 was greater than 90%.

Protocol Amendments

The Applicant's Description:

No changes were made in the conduct of the study or planned analyses. Study FP01C-13-001 was performed in accordance with study protocol FP01C-13-001, Version 1.4 (October 14, 2015) (Study FP01C-13-001, Section 9.8).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

8.1.2 Study Results

Compliance with Good Clinical Practices

Data / The Applicant's Position:

The Study FP01C-13-001 was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. (Study FP01C-13-001, Section 5.2.).

To ensure compliance with these procedures and to assess the adequacy of quality control procedures, Foresee Pharmaceuticals, Co., Ltd. undertook a GCP audit program. Audits were performed by (b) (4) that operated independently of the trial monitors. The audit program, together with the internal quality control procedures of QPS, provided reassurance that trial conclusions were based on valid procedures for data management and analysis, and that the clinical trial program was carried out in accordance with GCP guidelines (Study FP01C-13-001, Section 9.6).

The FDA's Assessment:
The FDA agrees that the study appears to have been conducted in compliance with Good Clinical Practices. The Informed Consent adequately and fairly explained the investigational and voluntary nature of the trial and the risks of participation

Financial Disclosure

Data:

The Applicant provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3455. No investigators had disclosable financial interests.

The Applicant's Position:
No concerns were raised regarding the overall integrity of the data.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Lawrence Gan, the President and CEO of Forsee Pharmaceuticals Co. Inc., submitted FDA Form 3454 stating the following:

> "I certify that I have not entered into any financial arrangement with the listed clinical investigators …[names attached]… whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a

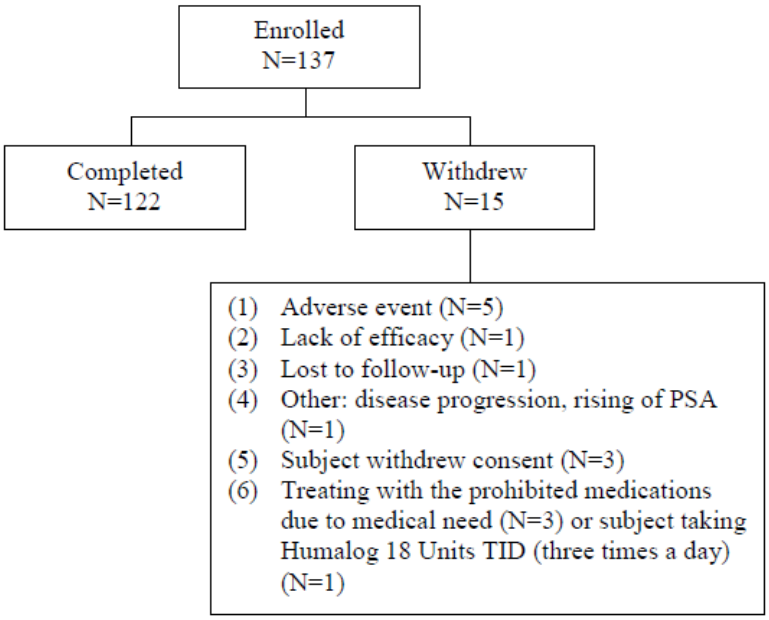
significantly equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

Patient Disposition

Data / The Applicant's Position:

There were 137 subjects enrolled in this study, including 33 subjects in Part I and 104 subjects in Part II. Of the 137 enrolled subjects, 15 (10.9%) subjects did not complete the study, including 5 subjects who terminated early due to adverse event, 3 subjects terminated early due to consent withdrawal, 3 subjects terminated early due to receiving prohibited medications for medical need, 1 subject terminated early due to lack of efficacy, 1 subject terminated earlier than scheduled due to other reason (disease progression, rising PSA), 1 subject terminated early due to protocol violation: subject took Humalog 18 Units TID (three times a day) and 1 subject was lost to follow up (see Applicant - Figure 4).

Applicant - Figure 4: Disposition of Patients



N = number of subjects
Source: Study FP01C-13-001

The FDA's Assessment:
The FDA confirmed the Applicant's summary of patient disposition using dataset ADSL, variable DSTERM. One hundred and twenty-two (89.1%) patients received at least two doses of study

drug and completed at least 336 days of study treatment.

APPEARS THIS WAY ON ORIGINAL

Protocol Violations/Deviations

Data / The Applicant's Position:

In Study FP01C-13-001, 452 protocol deviations were reported, of which 14 incidences in eleven subjects were reported as major deviations. The other 438 deviations were reported as minor based on the sponsor's internal guidance (for major protocol deviations, refer to Study FP01C-13-001, Section 10.2).

At one study site a major protocol violation due to improper storage condition for four investigational product packages occurred. However, none of these investigational product packages was used in subjects at this site (refer to Study FP01C-13-001, Section 10.2).

The FDA's Assessment:

Table 5 below summarizes all reported major protocol violations. In addition, the storage temperature of 4 IP kits (1395, 1396, 1397, 1398) at Site LT03 exceeded the allowed range; however, none of these IP packages was used. One patient ((b) (6)) discontinued study treatment because of a protocol violation.

After review, FDA concludes that none of these violations are likely to have significantly affected the overall efficacy or safety findings of the trial.

Table 5. FP01C-13-001 Major Protocol Violations

Subject No.	Visit	Description
(b) (6)	N/A	An SAE on (b) (6) was not reported within 24 hours. This SAE was reported on (b) (6) (b) (6)
	2	An incorrect kit of IP was administered (Kit 1437 was administered instead of Kit 1409).
	N/A	An SAE on (b) (6) was not reported within 24 hours.
	2	An incorrect kit of IP was administered (Kit 1409 was administered instead of Kit 1437).
	23	The patient refused his Early Termination visit and discontinued the trial on (b) (6).
	21	The patient used an exclusionary medication (docetaxel).
	15	The patient forgot to come to the clinic for Visit 15 (Day 169). He returned for Visit 16 (Day 170), reported no irritation to the injection site, and completed Visit 16 procedures.
	CM	The patient was hospitalized for an AE and was given two prohibited medications (prednisone and insulin).
	CM	The patient used a prohibited medication (insulin).
	9	On (b) (6), PK-A, PK-B, and PK-C samples were received unrequested and unfrozen for the patient's Day 28 visit. The patient returned to the site on (b) (6) to have PK samples redrawn.
	1	Serum creatinine of 1.6 mg/dL at screening did not meet Inclusion Criteria No.7 (serum creatinine ≤ 1.5 mg/dL). Creatinine was redrawn and met inclusion criteria.

Table of Demographic Characteristics

Data / The Applicant's Position:

The average age of the 137 subjects was 71.1 ± 8.7 years (mean ± SD), and all were male. Almost 90% of enrolled subjects were White (89.8%), followed by Black (5.8%), Asian (3.6%), and unknown (0.7%) (refer to NDA Module 2.7.3., Section 2.7.3.3.1; see Applicant - Table 3).

Applicant - Table 6: Summary of Demographics (ITT Population)

Variable / Status	**Part I** (N=33)	**Part II** (N=104)	**Total** (N=137)
Age (years)*[1]			
n	33	104	137
mean (SD)	73.5 (8.40)	70.3 (8.70)	71.1 (8.70)
median (min, max)	74.0 (54, 86)	70.0 (51, 88)	71.0 (51, 88)
Gender			
Male	33 (100.0%)	104 (100.0%)	137 (100.0%)
Ethnicity			
Hispanic	2 (6.1%)	1 (1.0%)	3 (2.2%)
Non - Hispanic	30 (90.9%)	31 (29.8%)	61 (44.5%)
Unknown	1 (3.0%)	72 (69.2%)	73 (53.3%)
Race			
Asian	4 (12.1%)	1 (1.0%)	5 (3.6%)
Black	4 (12.1%)	4 (3.8%)	8 (5.8%)
Unknown	0 (0.0%)	1 (1.0%)	1 (0.7%)
White	25 (75.8%)	98 (94.2%)	123 (89.8%)

*[1]Age was calculated as (Date of informed consent - Date of birth)/365.25 and round down to integer.
ITT = intent-to-treat; SD = standard deviation
Source: Main Study FP01C-13-001, Table 11-8 and Table 14.1.1

The patient baseline demographics in Study FP01C-13-001 are deemed representative for the target population.

The FDA's Assessment:
Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) indicate that risk factors for being diagnosed with and for dying of prostate cancer are older age, a family history of prostate cancer, and African American descent. Between 2014 and 2018, the annual incidence of prostate cancer for individuals of African-American descent was 175.2 per 100.000 persons, compared to 109.8 for individuals of all races. Corresponding death rates from prostate cancer were 37.4 and 19.0 per 100,000 persons, respectively.[5] Considering the incidence of and mortality from prostate cancer in African-Americans compared to Caucasians, the overall proportion of African-Americans enrolled is relatively small.

[5] https://seer.cancer.gov/statfacts/html/prost.html. Accessed December 9, 2020.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data / The Applicant's Position:

Males aged ≥ 18 years with histologically confirmed prostate carcinoma had a baseline morning serum testosterone level > 150 ng/dL at screening and an Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2 (refer to NDA Module 2.7.3., Section 2.7.3.3.1).

Subjects had a life expectancy of at least 18 months. Subjects were not to receive any chemotherapy, immunotherapy, cryotherapy, radiotherapy, or anti-androgen therapy concomitantly or within 8 weeks prior to screening for treating of prostate cancer. Vaccinations and major surgery within 4 weeks of screening were criteria for exclusion from the study. Subjects were not to receive any LHRH suppressive therapy, exogenous testosterone supplementation, or history or presence of hypogonadism within 6 months of screening. History or presence of Type I diabetes or Type II diabetes (unless only oral hypoglycemic required) were regarded as criteria for exclusion from the study (refer to NDA Module 2.7.3., Section 2.7.3.3.1).

The average duration with diagnosed prostate cancer was 4.9 ± 6.58 years. Approximately 50.4% of subjects had prostate carcinoma stage ≥ III, while approximately 25.5% of subjects had stage ≤ II; the stage status of the remainder of subjects was unknown. Regarding ECOG performance status, 83.2% of subjects were Grade 0 and 16.1% of subjects were Grade I (refer to NDA Module 2.7.3., Section 2.7.3.3.1).

The patient baseline characteristics in Study FP01C-13-001 as covered above are deemed representative for the target population and appropriate for demonstrating the efficacy of LMIS 50 mg as ADT in prostate cancer.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of other baseline characteristics. Thirty-two (23.4%) patients had stage IV prostate cancer, 27% locally advanced (T3/4 NX M0 or any T N1 M0), 26% localized (T1 or T2 N0 M0), and 24% not classifiable. The median testosterone concentration at baseline was 440 ng/dL.

Figure 5. Summary of Disease Characteristics at Baseline

Variable/Staus	Part 1 (N = 33)	Part 2 (N = 104)	Total (N = 137)
Stage			
I	1 (3.0%)	3 (2.9%)	4 (2.9%)
II	8 (24.2%)	23 (22.1%)	31 (22.6%)
III	5 (15.2)	32 (30.8%)	37 (27.0%)
IV	9 (27.3%)	23 (22.1%)	32 (23.4%)
Unknown	10 (30.3%)	23 (22.1%)	33 (24.1%)
ECOG performance status			
0	30 (90.9%)	84 (80.8%)	114 (83.2%)
1	3 (9.1%)	19 (18.3%)	22 (16.1%)
2	0	1 (1.0%)	1 (0.7%)
Serum testosterone (ng/dL)			
Mean ± SD	390 ± 144	499 ± 193	473 ± 188
Median (range)	410 (150, 755)	455 (229, 1100)	440 (150, 11)

Source: datasets ADSL and ADEA; variables STAGE, PARAM, BASE, PART

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data / The Applicant's Position:

Treatment compliance

Of 137 subjects enrolled in Study FP01C-13-001, 128 subjects received both doses of Camcevi™ 42 mg. The compliance was 93.4% (Study FP01C-13-001, Section 11.3). All subjects received Camcevi™ 42 mg via subcutaneous injection at the study site. The administration of the investigational product to the subject was under the supervision of the Investigator and controlled by the clinical site personnel (Study FP01C-13-001, Section 9.4.8).

Concomitant medication

The following therapies were allowed during Study FP01C-13-001:

1. Bisphosphonates
2. Denosumab
3. Supplementation of vitamin D and calcium (if, in the investigator's opinion, needed for patient's health)
4. Plain, over-the-counter multi-vitamins
5. Glucocorticosteroids (if being used as a replacement therapy)
6. Pain medication (if i an over-the-counter or prescription medication and prescribed by a physician)
7. Oral hypoglycemic drug for control of Type II diabetes
8. Radiation for pain control.

Any use of concomitant treatment was recorded in the Case Report Form (CRF) (Study FP01C-13-001, Section 9.4.7).

Rescue medication

Not applicable.

The FDA's Assessment:
The proportion of patients who received both doses of leuprolide injectable emulsion in FP01C-13-001 (128 of 137) is acceptable.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data / The Applicant's Position:

The primary efficacy endpoint was suppression of serum testosterone levels below castrate levels (≤ 50 ng/dL), an accepted surrogate endpoint for GnRH agonists in ADT of prostate cancer.

With respect to the primary efficacy endpoint, more than 98% of subjects had a serum testosterone level suppressed to castrate level by Day 28 following the first injection of Camcevi™ 42 mg. From Day 28 to the end of the study (Day 336), ≥ 97% of subjects had serum testosterone levels suppressed to the castrate level (see Applicant - Table 4) (Study FP01C-13-001).

Applicant - Table 7: Primary Endpoint Results for Main Study FP01C-13-001

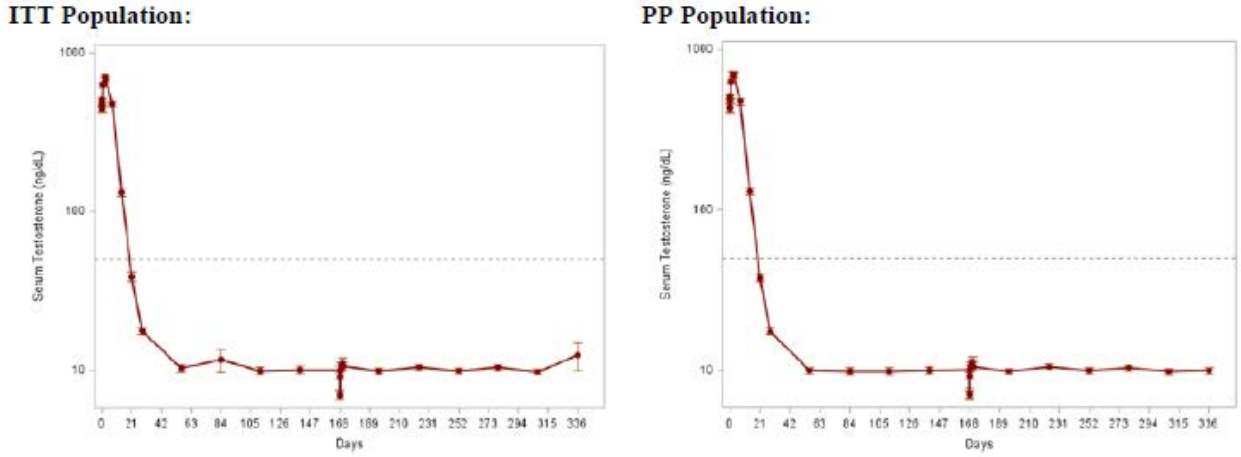
Population	# Enrolled/ completed	Percentage of subjects with serum testosterone ≤ 50 ng/dL (95% CI)	
		By Day 28	Day 28–Day 336
ITT[a]	137/137	98.5 (94.8–99.8)	97.0 (92.2–98.9)
PP[b]	137/124	99.2 (95.6–100.0)	97.6 (92.7–99.2)

[a] Any subject who received at least 1 dose of LMIS 50 mg (Camcevi™ 42 mg)
[b] Any subject who received 2 doses of LMIS 50 mg, followed the inclusion/exclusion criteria of the protocol, and had no major protocol violation
CI = confidence interval; ITT = intent-to-treat; PP = per protocol
Source: Main Study FP01C-13-001, Table 11-9 and Table 11-10

Sensitivity analyses revealed that the suppression rate was 97.0% (95% CI: 92.2-98.9) for the ITT population, 97.6% (95% CI: 92.7- 99.2) for the PP population, and 97.4% (95% CI: 92.3-99.2) for completed cases. All lower 95% confidence interval bounds for the suppression rate were greater than 90% (Study FP01C-13-001).

At 7 to 8 weeks after the first Camcevi™ 42 mg injection, the mean serum testosterone level reached a plateau of approximately 10 ng/dL (Applicant - Figure 5). Serum testosterone remained at this level until the end of the study at Week 48 (Day 336). These data demonstrated the efficacy of two separate doses of Camcevi™ 42 mg in suppressing and maintaining the serum testosterone below the pre-defined and accepted castrate level of ≤ 50 ng/dL (Study FP01C-13-001).

Applicant - Figure 6: Serum Testosterone Over Time (Study FP01C-13-001)



ITT = intent-to-treat; PP = per protocol
Source: Main Study FP01C-13-001, Figure 11-3 and Figure 11-4

The FDA's Assessment:

FDA Guidance for Industry on Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone (GnRH) Analogues (https://www.fda.gov/media/129027/download) discusses phase 3 efficacy trial considerations. Among trial design features discussed is the fact that plasma testosterone level can be used as a validated surrogate endpoint to assess the efficacy of GnRH analogues, and that a testosterone level < 50 ng/dL is considered castrate level. As GnRH agonists are expected to achieve castrate testosterone levels by Day 28, the guidance states that testosterone levels should be measured at that time. The primary analysis for the single-arm trial described in the guidance is the Kaplan-Meier estimate of the proportion of patients who achieve and maintain castrate testosterone levels (< 50 ng/dL) from Day 28 through the end of the treatment period. To demonstrate efficacy, the lower bound of the 95% confidence interval for this estimate should be greater than 90% (i.e., fewer than 10% treatment failures).

The FDA confirmed the information presented in Applicant - Table 7: Primary Endpoint Results for Main Study FP01C-13-001 above using dataset ADEA (variables PARAM and AVALC). Study FP01C-13-001 met its primary endpoint as demonstrated by the Kaplan-Meier estimate of the lower bound of the 95% CI for the proportion of patients who achieved and maintained castration testosterone levels from Day 28 through Day 336, being above 90%. The percentage of patients with testosterone suppression (≤ 50 ng/dL) from week 4 through week 48 was also described in section 14 of the USPI, and was 97.0% (133/137; 95% CI: 92.2-98.9) estimated using the Kaplan-Meier method. This analysis is per the FDA guidance on developing GNRH analogues. Section 14 also includes the percentage of patients with testosterone suppression to

≤ 20 ng/dL on Day 28, 69.3% (95/137).

The FDA guidance specified a testosterone level < 50 ng/dL as the primary endpoint for a trial intended to support approval, and study FP01C-13-001 used a ≤ 50 ng/dL endpoint. There was one patient with a testosterone level of exactly 50 ng/dL; see *sensitivity analysis #3* below which defines castration as <50 ng/dL instead of ≤ 50 ng/dL to account for this difference.

Section 14 of the USPI describes these results in the text using the ITT population (n = 137), not using the subgroup that (n=122) completed the study per protocol. We note that the per protocol population of n=124 as described in Applicant - Table 7: Primary Endpoint Results for Main Study FP01C-13-001 above is not the same as the 122 patients who completed the study; the Applicant's definition of the per protocol population is "any subject who received 2 doses of leuprolide injectable emulsion 50 mg, followed the inclusion/exclusion criteria of the protocol, and had no major protocol violation".

The review team identified 3 patients whose Day 28 assessment occurred on Day 30, 32, or 34, which was out of the pre-specified 1 day visit window for the Day 28 assessment. The observed testosterone levels for these patients were under 50 ng/dL at both the previous assessment (Day 21 assessment) and at the delayed Day 28 assessment that occurred at Day 30-34. The fact that these 3 patients had assessments that were not on the protocol-specified date was described in section 14 of the USPI when the Study FP01C-13-001 results were presented, after which "+/-7 days" was added in parenthesis after "Week 4" in the sentence, "Serum testosterone levels were suppressed to ≤50 ng/dL by Week 4 in 98.5% of the patients…". Although three of these assessments were not on the protocol-specified Day 28, the FDA review team felt that the timing being delayed by 2-6 days in these few patients overall was within clinical range of acceptability, and the fact that testosterone suppression had already been achieved at the previous assessment and was maintained at the delayed assessment was reassuring. Thus the review team agreed that those 3 patients should be considered as having achieved castration at Day 28 overall.

Table 8 summarizes details regarding castration failures and reasons for censoring.

Table 8. FP01C-13-001 Castration Failures and Censoring Reasons (ITT Population)

Outcome	LMIS (N=137)
Castration failure events, n (%)	4 (3)
Non-castration T level at Day 28 (+1 day)	2 (1)
Non-castration T level between Day 28 and Day 336	2 (1)
Censored, n (%)	
Missing 2 or more consecutive visits[a]	1 (<1)
Early study discontinuation	14 (10)

End of study visit	118 (86)

[a] Patient had castration testosterone level before and after the missing visits
Source: ADTTE.XPT

One patient had more than 2 consecutive missing visits, and testosterone levels were ≤ 50 ng/dL immediately before and after the missing assessments. This patient was censored at his last testosterone assessment before the missing data per the censoring rules specified in the Statistical Analysis Plan and the FDA's draft guidance on GnRH product development mentioned above. An additional 4 patients had only one testosterone assessment missing and the testosterone levels were ≤ 50 ng/dL immediately before and after the missing assessment. Therefore, the differences in censoring rules specified in the SAP and the FDA's draft guidance regarding handling patients with missing assessments (see FDA's assessment on Study Endpoints) do not affect the outcomes.

Sensitivity analyses on the primary efficacy endpoint performed by the Applicant are presented in Table 9. Results are consistent with the primary findings.

Table 9. FP01C-13-001 The Applicant's Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity Analysis	Description	Castration Rate % (95% CI)
1	In the per-protocol population (n=124)	97.6 (92.7, 99.2)
2	Censoring patients with any missing if no prior escape in the ITT population	97.0 (92.2, 98.9)
3	Censoring patients with any missing if no prior escape in the per-protocol population	97.4 (92.3, 99.2)
4	In patients who completed the study and no testosterone data missing from D28 through D336 (n=117)	97.4 (92.3, 99.2)

[Source: ADTTE.XPT]

The FDA conducted additional sensitivity analyses to evaluate the robustness of the observed primary results:

Sensitivity Analysis 1: Per above, three patients completed their Day 28 assessments on Days 30, 32, or 34, respectively, which was out of the pre-specified 1-day window for this assessment. In the primary efficacy analysis, those 3 patients were considered as having achieved serum testosterone levels ≤ 50 ng/dL at Day 28 because their serum testosterone levels were ≤ 50 ng/dL at the previous assessment (Day 21) and the delayed Day 28 assessment occurred at Day 30-34. Sensitivity Analysis 1 considered these three patients whose Day 28 assessment occurred between Days 30 and 34 as having missed their Day 28 assessments.

Therefore, per the analysis rules specified in Table 4, these three patients were handled as having an event on Day 28. At Day 28, 96.4% (95% CI: 91.7, 98.8) of patients had a serum testosterone level suppressed to ≤ 50 ng/dL. From Day 28 to Day 336, 94.8% (95% CI: 89.5, 97.5) of patients achieved and maintained testosterone level of ≤ 50 ng/dL.

Sensitivity Analysis 2: Fifteen (10.9%) of 137 patients in the ITT population discontinued the study before Day 336. Of those 15 patients, 14 had serum testosterone concentrations ≤ 50 ng/dL at their last assessments. Sensitivity Analysis 2 considers those 14 patients as having had events at their next scheduled assessment day. The percentage of patients achieving and maintaining castration from Day 28 through Day 336 was 86.8% (95% CI: 79.9, 91.5).

Sensitivity Analysis 3: This sensitivity analysis defines castration as <50 ng/dL instead of ≤ 50 ng/dL. One patient was affected by changing the cutoff. Per the <50 ng/dL cutoff, the percentage of patients achieving and maintain castration from Day 28 through Day 336 was 96.3% (95% CI: 91.3, 98.4).

At the FDA's request, the Applicant conducted a sensitivity analysis in which patients who had received concomitant medications and herbal supplements that could affect serum testosterone levels were censored at Day 28. The applicant identified 10 such patients. The percentage of patients who achieved and maintained serum testosterone levels ≤ 50 ng/dL from Day 28 through Day 336 was 96.9% (95%CI: 91.8, 98.8) after censoring those 10 patients.

Results of these sensitivity analyses are consistent with those of the primary analysis except for Sensitivity Analysis 2 where the castration rate point estimate was < 90%. In this sensitivity analysis, patients who discontinued study early were considered as events. A total of 14 additional events were added in this sensitivity analysis. The reasons for early study discontinuation included adverse events (n=5), withdrawal of consent (n=3), treated with the prohibited medications due to medical need (n=3), lost to follow-up (n=1), received Humalog 18 units TID (n=1), and other (n=1). Considering early discontinuation as an event is considered as a conservative approach; therefore, the FDA reviewers concluded that the lower sustained castration rate estimated in the sensitivity analysis 2 is not a concern.

Data Quality and Integrity

Data / The Applicant's Position:

A total of six interim analyses (5 interim safety reviews and 1 interim analysis of efficacy) were conducted during Study FP01C-13-001. The interim analyses were overseen by an Independent Data Monitoring Committee and an Independent Statistical Center.

The objective of these safety interim analyses was to assess the feasibility of continuing with Camcevi™ 42 mg after assessment of safety in those 33 subjects. The recommendation was to continue the trial as planned. The interim analysis was also conducted when 100 subjects completed the Day 28 visit. The objective of this interim analysis was to assess the feasibility of continuing Camcevi™ 42 mg with regard to efficacy and also to re-assess the total sample size based on observed dropout rate and the castration rate on Day 28 (Report FP01C-13-001, Section 11.4.2.3).

In the above interim analysis, 100 subjects were included and the castration rate based on serum testosterone levels on Day 28 was 98% (95% CI: 93.0-99.8). The estimated conditional power was 99.07%. Thus, the trial continued as planned with the current sample size (Study FP01C-13-001, Section 11.4.2.3).

In all, the data quality and integrity is considered appropriate and not compromised by the pre-specified interim analyses.

The FDA's Assessment:
The overall data quality and integrity were acceptable and reliable to support regulatory decision making.

Efficacy Results – Secondary and other relevant endpoints

Data / The Applicant's Position:

Secondary endpoints included post-suppression elevation of serum testosterone (> 50 ng/dL), serum PSA levels, and serum LH levels. PSA and LH provide additional assessments of efficacy, as PSA is a marker for prostate cancer and prostate cancer control and LH production is upstream of testosterone (Study FP01C-13-001).

Post-supression elevation of serum testosterone

With regard to post-suppression elevation of serum testosterone to > 50 ng/dL evaluated as secondary endpoint, two subjects (2/137, 1.5%) exhibited post-suppression serum testosterone levels above the castrate threshold (> 50 ng/dL) during the study after reaching testosterone castrate levels on Day 28. Both were due to the 'acute-on-chronic surge' following the second administration of Camcevi™ 42 mg. However, the percentage of subjects exhibiting post-suppression elevation of serum testosterone was 0% in both the ITT and PP population at the end of the study (Day 336) (Study FP01C-13-001).

Testosterone concentration-time profiles were similar when sub-analysed for race, age, and body weight (PK Report FSEE-CSC-101).

Implementing a more stringent criteria (see e.g. Hoda et al., 2017; Klotz et al., 2015), the efficacy of two separate doses of LMIS 50 mg was further analysed by examining the percentage of subjects with serum testosterone levels < 20 ng/dL on Day 28 and Day 336. Of 135 subjects who achieved the pre-defined castrate level (≤ 50 ng/dL), 95 subjects (95/135, 70.4%) showed a serum testosterone level < 20 ng/dL on Day 28. On Day 336, all subjects who completed the study (122/122) achieved castrate levels (≤ 50 ng/dL), among which 117 subjects (117/122, 95.9%) showed serum testosterone levels < 20 ng/dL (Study FP01C-13-001).

Effect on Serum LH

The effect of Camcevi™ 42 mg on serum LH levels was also examined. The data demonstrated that the administration of Camcevi™ 42 mg significantly reduced serum LH levels after its first injection and this effect remained until the end of study (Study FP01C-13-001).

Effect on Serum PSA

The administration of Camcevi™ 42 mg significantly reduced the serum PSA levels after the first injection, and the effect remained until the end of the study (Applicant - Table 5) (Study FP01C-13-001).

Applicant - Table 10: Prostate-specific Antigen Levels Over Time (Study FP01C-13-001)

	Serum PSA levels (ng/mL), Mean ± SD					
	Baseline	Day 28	Day 84	Day 168	Day 252	Day 336
ITT[a]	84.747±382.4744	21.709±80.9601[#]	5.017±18.4060[#]	2.577±7.5404[#]	3.545±13.0604[#]	12.837±65.5957[#]
PP[b]	70.240±333.4071	18.040±64.3671[#]	3.575±9.7538[#]	2.641± 7.6833[#]	3.620±13.2136[#]	7.972±37.1654[#]

[a]Any subject who received at least 1 dose of LMIS 50 mg
[b] Any subject who received 2 doses of LMIS 50 mg, met the inclusion/exclusion criteria of the protocol, and had no major protocol violation
[#]p < 0.001
ITT = intent-to-treat; PP = per protocol; PSA = prostate-specific antigen
Source: Main Study FP01C-13-001, Table 11-12

A mild rebound in PSA levels was observed from Day 252 to Day 336; however, the mean serum levels remained low and significantly lower than the baseline value (Study FP01C-13-001).

A post-hoc analysis was performed in the subjects with elevated PSA at baseline. There were 99 of 137 subjects (72.3%) who had elevated PSA (> 4 ng/mL) at baseline, and there appeared to be a trend with the progressive reduction of PSA levels toward the end of study (Study FP01C-13-001).

In all, Study FP01C-13-001 demonstrates that subcutaneous injection of Camcevi™ 42 mg at 6-month intervals effectively suppresses serum testosterone levels below the castrate threshold (≤ 50 ng/dL) by Day 28. This suppressive effect of Camcevi™ 42 mg was maintained from Day 28 to Day 336 following the second injection of Camcevi™ 42 mg on Day 168 in both

the ITT and PP populations. If applying a more stringent castration threshold criteria (< 20 ng/mL), it is shown that the first Camcevi™ 42 mg dose effectively suppresses serum testosterone below < 20 ng/dL in 70% of subjects on Day 28, and serum testosterone suppression was maintained to the end of study (Day 336) after the second Camcevi™ 42 mg injection on Day 168 in more than 95% of subjects who completed the study.

Serum PSA levels were significantly reduced from Day 28 until the end of study. Although a mild rebound in PSA levels was observed from Day 252 to Day 336, the mean serum PSA levels remained low and significantly lower than the baseline value.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the results of secondary endpoints and that these results are generally supportive of the activity of leuprolide injectable emulsion. The FDA also calculated percentage change of serum PSA levels from baseline, as shown in Table 11.

Table 11 Change in Serum PSA Levels from Baseline Over Time

Timepoint	N	Relative Change from Baseline (mean ± SD)
Baseline	137	--
Day 28	137	-50.6% ± 80.9
Day 84	136	-83.3% ± 24.6
Day 168	129	-87.3% ± 22.9
Day 252	124	-86.3% ± 26.5
Day 336	131	-79.4% ± 50.4

[Source: ADEA.XPT]

Section 14 of product labeling reports these results in text form and states that PSA levels were lowered on average by 51% after 4 weeks, 83% after 3 months, and remained suppressed throughout the 48 weeks of treatment.

Dose/Dose Response

Data / The Applicant's Position:
Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

In accordance with other approved leuprolide depot forms suitable for 6-monthly administration in the palliative treatment of prostate cancer, Camcevi™ 42 mg is proposed to be dosed subcutaneously in 6-month intervals (42 mg leuprolide base every 6 months) (refer to NDA Module 2.5, Section 2.5.1).

The dosage strength of Camcevi™ 42 mg is equivalent to comparable, approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg), each

containing 42 mg of leuprolide base, and the proposed dosing schedule for Camcevi™ 42 mg (42 mg leuprolide base every 6 months per subcutaneous injection) corresponds with approved leuprolide acetate depot forms for 6-monthly subcutaneous administration (such as Eligard® 45 mg) (refer to NDA Module 2.5, Section 2.5.1).
In all, the dose response (serum testosterone suppression, effects on serum LH and PSA levels) after subcutaneous administration of Camcevi™ 42 mg corresponds with similar approved 6-month depot leuprolide (acetate) forms (e.g., Crawford et al., 2006).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Study FP01C-13-001 evaluated only the 42 mg dose of leuprolide injectable emulsion.

Durability of Response

Data / The Applicant's Position:

At 7 to 8 weeks after the first Camcevi™ 42 mg injection, the mean serum testosterone level reached a plateau of approximately 10 ng/dL (Applicant - Figure 5). Serum testosterone remained at this level until the end of the study at Week 48 (Day 336), which is in accordance with observations made with other leuprolide (acetate) 6-month depot forms for subcutaneous administration (e.g., Crawford et al., 2006).

For Camcevi™ 42 mg, no patients have been assessed for efficacy for dosing durations longer than 1 year. The percentage of subjects with testosterone suppression through the end of Study FP01C-13-001 (Day 336) was 97.0% (133/137 subjects) in the ITT population and 97.6% (121/124 subjects) in the PP population. No subjects exhibited post-suppression elevations of serum testosterone at Day 336. Serum levels of PSA and LH were also significantly reduced at this timepoint (refer to NDA Module 2.7.3., Section 2.7.3.5.).

The FDA's Assessment:
FP01C-13-001 assessed for efficacy for a dosing duration of one year. This duration is adequate to assess efficacy, as it is in line with the median progression-free survival of men with metastatic hormone-sensitive prostate cancer following institution of androgen deprivation therapy.[6,7]

[6] Kyriakopoulos, CE, Chen Y-H, Carducci MA, et al. Chemohormonal Therapy In Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol 2018 ;36:1080.
[7] James ND, Spears MR, Clarke NW, et al. Survivial with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Onco 2015;67:2018.

Persistence of Effect

Data / The Applicant's Position:

No patients have been assessed for efficacy for dosing durations of Camcevi™ 42 mg longer than 1 year. The percentage of subjects with testosterone suppression through the end of Study FP01C-13-001 (Day 336) was 97.0% (133/137 subjects) in the ITT population and 97.6% (121/124 subjects) in the PP population. No subjects exhibited post-suppression elevations of serum testosterone at Day 336 (refer to NDA Module 2.7.3. Section 2.7.3.5.).

After cessation of leuprolide, serum testosterone levels will gradually rise after a certain period of time.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Serum testosterone levels are expected to rise after cessation of leuprolide injectable emulsion. The kinetics this expected rise have not been formally studied.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data / The Applicant's Position:

Not applicable.

Please refer to the secondary outcomes mentioned in the section "**Efficacy Results – Secondary and other relevant endpoints**" of the Section 8.1.2 above.

The FDA's Assessment:
Clinical outcome assessments and patient reported outcomes were not formally collected as part of FP01C-13-001

Additional Analyses Conducted on the Individual Trial

Data / The Applicant's Position:

No additional efficacy analyses were conducted for Camcevi™ 42 mg; for PK analyses, refer to Section 6.2.1.

The FDA's Assessment:
Two subjects (1.5%) exhibited transient post-suppression serum testosterone levels > 50 ng/mL on Days 169 and/or 170 which may be attributed to what has been termed a "surge" or "acute on chronic" phenomenon. (b) (4)

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:
This NDA is supported by one single arm clinical trial (FP01C-13-001) in which leuprolide injectable emulsion was administered to 137 patients on Days 0 and 168, and testosterone levels were measured at regular intervals from Day 28 through Day 336. The primary objective was to demonstrate the ability of leuprolide injectable emulsion to achieve a serum testosterone level ≤ 50 ng/dL by Day 28 and maintained through Day 336. In the primary efficacy analysis, 97% (95% CI: 92.2, 98.9) of patients maintained serum testosterone levels ≤ 50 ng/mL between Day 28 and 336, estimated by the Kaplan-Meier method. The trial met this primary efficacy endpoint, as the lower bound of the 95% CI was 92.2%. Sensitivity analyses of the primary efficacy endpoint were generally in line with the primary analysis. With regard to secondary efficacy endpoints, leuprolide injectable emulsion suppressed serum testosterone below the more stringent threshold of 20 ng/dL in 69% of subjects by Day 28, reduced mean serum LH levels by approximately 90%, confirming that the therapeutic effect is achieved by inhibiting LH release, and reduced serum PSA levels. This trial and its efficacy analyses generally followed the recommendations outlined in the FDA Guidance for Industry on Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone (GnRH) Analogues (https://www.fda.gov/media/129027/download).

8.1.4 Assessment of Efficacy Across Trials

Primary Endpoints

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

The Sponsor conducted a single pivotal Phase 3 trial to evaluate the efficacy and safety of Camcevi™ 42 mg. Study FP01C-13-001 was a multicenter, open label, single-arm study conducted in 137 male patients with prostate carcinoma.

Apart from the safety extension Study FP01C-13-001-EX, evaluating safety only, no further clinical study has been conducted with Camcevi™ 42 mg.

Therefore, no efficacy assessment of Camcevi™ 42 mg with respect to primary endpoints across trials can be carried out.

For comparison of single-arm Camcevi™ 42 mg Study FP01C-13-001 with published clinical trials on other approved leuprolide (acetate) depot forms (external controls), refer to Section 8.1.5 below.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Secondary and Other Endpoints

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

The Sponsor conducted a single pivotal Phase 3 trial to evaluate the efficacy and safety of Camcevi™ 42 mg. Study FP01C-13-001 was a multicenter, open label, single-arm study conducted in 137 male patients with prostate carcinoma.

Apart from the safety extension Study FP01C-13-001-EX, evaluating safety only, no further clinical study has been conducted with Camcevi™ 42 mg.

Therefore, no efficacy assessment of Camcevi™ 42 mg with respect to secondary and other endpoints across trials can be carried out.

For comparison of single-arm Camcevi™ 42 mg Study FP01C-13-001 with published clinical trials on other approved leuprolide (acetate) depot forms (external controls), refer to Section 8.1.5 below.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Subpopulations

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

The Sponsor conducted a single pivotal Phase 3 trial to evaluate the efficacy and safety of Camcevi™ 42 mg. Study FP01C-13-001 was a multicenter, open label, single-arm study conducted in 137 male patients with prostate carcinoma. Pre-specified efficacy analysys by sub-populations were not performed.

Apart from the safety extension Study FP01C-13-001-EX, evaluating safety only, no further clinical study has been conducted with Camcevi™ 42 mg.

Therefore, no efficacy assessment of Camcevi™ 42 mg with respect to sub-populations can be carried out.

For comparison of single-arm Camcevi™ 42 mg Study FP01C-13-001 with published clinical trials on other approved leuprolide (acetate) depot forms (external controls), refer to Section 8.1.5 below.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

A forest plot of subgroup/subpopulation analyses for castration rate achieved and maintained from day 28 through day 336 of Study FP01C-13-001 are presented in Figure 7. No apparent outliers are observed.

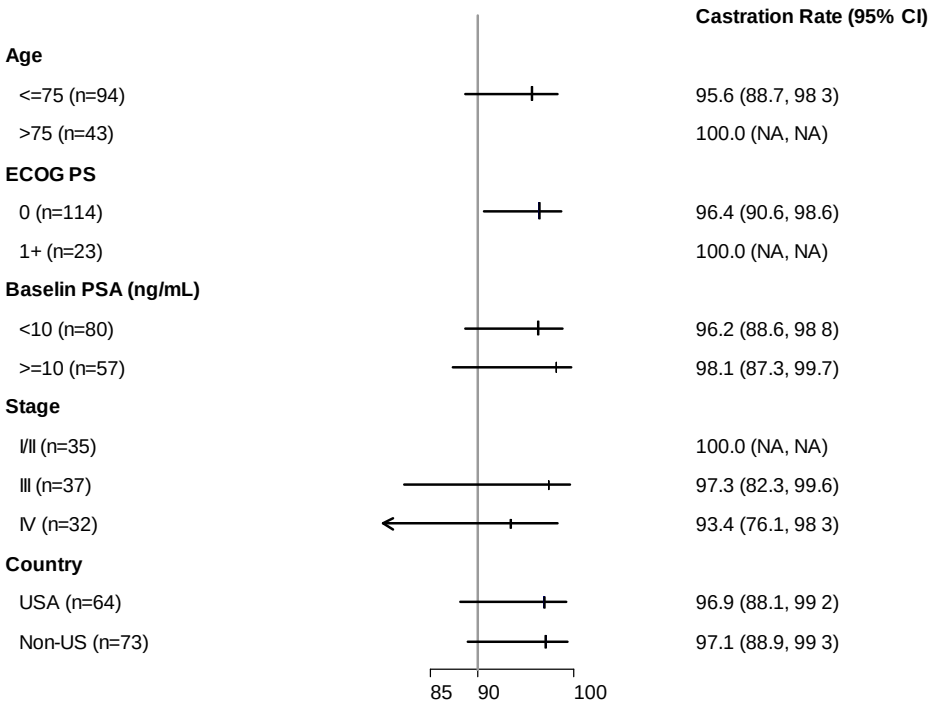


Figure 7 Forest Plot of Subgroup Results on Castration Rate

[Source: datasets adea.xpt, adsl.xpt, adqs.xpt]

Additional Efficacy Considerations

The FDA's Assessment:
Not applicable.

8.1.5 Integrated Assessment of Effectiveness

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

The Sponsor conducted a single pivotal Phase 3 trial to evaluate the efficacy and safety of Camcevi™ 42 mg. Study FP01C-13-001 was a multicenter, open label, single-arm study conducted in 137 male patients with prostate carcinoma.

Study FP01C-13-001 demonstrates that subcutaneous injection of Camcevi™ 42 mg at 6-month intervals effectively suppresses serum testosterone levels below the castrate threshold (≤ 50 ng/dL). Camcevi™ 42 mg effectively suppresses serum testosterone below the more stringent castrate threshold level of 20 ng/dL in 70% of subjects on Day 28 post injection and serum testosterone suppression was maintained to the end of study after the second Camcevi™ 42 mg injection in more than 95% of subjects. Serum PSA levels were significantly reduced from Day 28 until the end of study, indicating suitable disease control. Camcevi™ 42 mg significantly reduced the mean serum LH levels by approximately 98% as compared to baseline, confirming that the therapeutic effect of Camcevi™ 42 mg is achieved by inhibiting LH release.

Additionally, studies from published literature are supportive for the efficacy of 6-month leuprolide depot forms like Camcevi™ 42 mg in the palliative treatment of prostate cancer. A PubMed search was conducted to identify published studies with efficacy and safety information related to the proposed indication for 6-month leuprorelin depot forms. Five non-comparative, open-label studies were identified, all of which evaluated at least PD as per effects of two injections of 45-mg leuprolide acetate depot forms on serum testosterone levels over 12 months (48 weeks; see Applicant - Table 6 overleaf). These studies were comparable with Study FP01C-13-001 on Camcevi™ 42 mg. These published studies support the use of 6-month leuprolide depot formulations in ADT of prostate cancer. All studies evaluated the PD efficacy of 2 doses of 45-mg leuprolide depot for 12 months (48 weeks). A suppression in serum testosterone levels to below castrate levels (≤ 50 ng/dL) was reported for all of these studies in at least 93% of patients (Crawford et al., 2006; Spitz et al., 2012; Mostafa et al., 2014; Shore et al., 2017). The highest percentage reported was 99%, where 102 of 103 patients were below castrate levels (Crawford et al., 2006). For studies that used a more rigorous threshold of ≤ 20 ng/dL, 86.0% to 94.1% of patients were suppressed to below these levels through the end of the 12-month period (Crawford et al., 2006; Spitz et al., 2012; Shore et al., 2017). One of these studies analysed serum testosterone suppression by subgroups based on tumour node metastasis, body mass index, and race (Spitz et al., 2012). There was a significant difference between subjects with stage IV prostate cancer compared to those with stage II prostate cancer, with subjects of more advanced prostate cancer (stage IV) showing a higher rate of response to treatment (100% vs 91.8%, p = 0.003).

The percentage of patients with suppression of testosterone below castrate levels in the published literature is similar to the results obtained in the Sponsor-conducted Study FP01C-13-001 on Camcevi™ 42 mg, demonstrating that Camcevi™ 42 mg is efficacious as ADT in prostate cancer and provides the advantage to represent a more convenient ready-to-use formulation for clinical practice.

This is further supported by the scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from Camcevi™ 42 mg (Study FSEE CSC 100); the

follow-on leuprolide depot forms were all developed with reference to the first leuprolide form, Lupron® 1 mg.

Overall, the Sponsor has demonstrated that Camcevi™ 42 mg is effective in suppressing serum testosterone levels in ADT of prostate cancer at a degree comparable with other, approved leuprolide depot formulations.

Applicant - Table 12: Efficacy Data for Prostate Carcinoma Patients Treated With Leuprolide Acetate 45 mg, 6-month Depot Formulations From Published Literature Studies

Reference	Treated Population	Dose	Treatment Duration	Efficacy Findings
(Tunn, 2011; Ohlmann and Gross-Langenhoff, 2018)	n = 1273 mean age 75 years (range 50–97)	Eligard® 45 mg, SC injection, once every 6 months	12 months	• Median PSA values decreased by 94% from 11.6 to 0.7 ng/mL in the first 6 months. PSA decreased even further to 0.5 ng/mL at the end of the study (a 96% decrease). • Testosterone measurements were available for 350 patients. Median concentrations decreased from 89 to 10 ng/dL during the first 6 months, decreased even further to 9 ng/dL at the end of the study (a 90% decrease).
(Shore et al., 2017)	n = 111 mean age 73.2 years (range 53–84)	Eligard® 45 mg SC injection, once every 6 months	48 weeks	• Mean testosterone concentrations were decreased from 367.7±13.0 ng/dL at baseline to 16.7±3.4 at 1 month, 10.4±0.5 at 3 months, 10.4±0.5 at 6 months, and 12.6±2.1 at the end of the study. Four patients (3.6%) were above the castrate threshold at the end of the study. • LH concentrations were consistently below 1 IU/L by day 7 through the remainder of the study. • PSA baseline values were reduced by 97% at the end of the study.
(Spitz et al., 2012; Spitz et al., 2016)[a]	n = 148 mean age 74.9 years (range 48–84)	Leuprolide acetate 45 mg, intramuscular injection, o leuprolide injectable emulsion nce every 24 weeks	48 weeks	• Of the original 151 patients, 148 were included for the efficacy analysis. • Serum testosterone was suppressed to below castrate levels (50 ng/dL) from week 4 through week 48 in 93.4% of subjects. At 48 weeks, 94.1% were suppressed ≤ 20 ng/dL. Levels remained ≤ 11 ng/dL at the end of each treatment cycle. Of the 8 testosterone escapes, 4 occurred in patients who were African American and none were associated with increases in PSA. • Subjects with more advanced prostate cancer (stage IV) had a significantly higher rate of response to treatment (100% vs 91.8%, p = 0.003).

Reference	Treated Population	Dose	Treatment Duration	Efficacy Findings
				• At baseline, 75% of subjects had baseline serum PSA concentrations that were > 4 ng/mL. There was a transient rise in mean serum PSA concentrations after the first injections. Within 14 weeks, 87.4% of these subjects achieved a PSA of ≤ 4 ng/mL. At all subsequent visits, at least 86% of the subjects had a PSA of ≤ 4 ng/mL.
(Mostafa et al., 2014)[a]	n = 302 mean age 75.8 years (range 56–92)	Leuprolide acetate 45 mg (2 unspecified formulations, A and B), subcutaneous injection, once every 6 months	48 weeks	• The concentration-time profile for testosterone and LH for both formulations showed an initial increase after the first injection. • Testosterone and LH concentrations decreased continuously to reach a low plateau by week 4, which was maintained through the end of the study. There were no changes in concentrations with the second leuprolide acetate injections. The mean percentage of subjects that showed suppression of serum testosterone ≤ 50 ng/dL from week 4 through 48 was 93.4% (90% confidence interval 89.9–96.9) for formulation A. • A larger number of subjects receiving formulation B escaped from testosterone suppression and that arm of the study was prematurely terminated.
(Crawford et al., 2006)	n = 111 mean age 73.2 years (range 50–86)	Eligard® 45 mg, subcutaneous injection, once every 6 months	12 months	• Of the original 111 patients, 103 completed the 12-month study. • Mean time to castrate suppression was 21.2 days (median 21). At study completion, 102/103 patients (99%) were below medical castrate testosterone levels, with 91/103 (88%) less than 20 ng/dL. • Mean LH decreased from 6.98 ± 0.48 mIU/mL at baseline to below baseline by day 7. Mean LH then decreased consistently throughout the first 19 weeks to 0.1 ± 0.01 mIU/mL at day 133. LH levels at month 12 were 0.23 ± 0.14 mIU/mL. • Mean PSA decreased 97% from 39.8 ± 21.5 ng/mL at baseline to 1.2 ± 0.3 ng/mL at 12 months.

[a] The patients in (Mostafa et al., 2014) and (Spitz et al., 2012) overlap.
AE = adverse event; FSH = follicle-stimulating hormone; LH = luteinising hormone; PSA = prostate specific antigen; SAE = serious adverse event;

SC = subcutaneous; SD = standard deviation
Source: NDA Module 2.7.3., Section 2.7.3.6.

APPEARS THIS WAY ON ORIGINAL

The FDA's Assessment:

This NDA is supported by one single arm clinical trial (FP01C-13-001) in which leuprolide injectable emulsion was administered to 137 patients on Days 0 and 168, and testosterone levels were measured at regular intervals from Day 28 through Day 336. The primary objective was to demonstrate the ability of leuprolide injectable emulsion to achieve a serum testosterone level ≤ 50 ng/dL by Day 28 and maintained through Day 336. In the primary efficacy analysis, 97% (95% CI: 92.2, 98.9) of patients maintained serum testosterone levels ≤ 50 ng/mL between Day 28 and 336, estimated by the Kaplan-Meier method. The trial met this primary efficacy endpoint, as the lower bound of the 95% CI was 92.2%. Sensitivity analyses of the primary efficacy endpoint were generally in line with the primary analysis. Exploratory subgroup/subpopulation analyses of the primary efficacy endpoint were generally consistent with results in the overall population. With regard to secondary efficacy endpoints, leuprolide injectable emulsion suppressed serum testosterone below the more stringent threshold of 20 ng/dL in 69% of subjects by Day 28, reduced mean serum LH levels by approximately 90%, confirming that the therapeutic effect is achieved by inhibiting LH release, and reduced serum PSA levels. This trial and its efficacy analyses generally followed the recommendations outlined in the FDA Guidance for Industry on Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone (GnRH) Analogues (https://www.fda.gov/media/129027/download).

8.2 Review of Safety

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

Leuprolide (as an acetate salt) has been approved for the palliative treatment of prostate cancer in the United States since 1985 (Lupron® Injection; NDA 019010; AbbVie, Inc.). For this NDA, Foresee conducted one 12-month Phase 3 study (Study FP01C-13-001) with a 12-month safety extension (Study FP01C-13-001-EX) to evaluate the safety and efficacy of Camcevi™ 42 mg. The Sponsor established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from Camcevi™ 42 mg (Study FSEE-CSC-100) and intends to rely on the clinical and nonclinical safety of Lupron® (refer to NDA Module 2.5.1).

In addition, the information available in the published literature supporting the safety of 6-month leuprolide acetate depots was reviewed. A thorough PubMed search was performed on 20 September 2018 and limited to humans. Literature was evaluated based on level of evidence, with placebo-controlled trials as the highest level of evidence, followed by active-controlled studies, then blinded trials with patients randomized to different groups, followed by prospective studies that did not include randomization or blinding, then retrospective studies

or any relevant case reports. Results obtained from the analysis of clinical safety information identified 5 safety studies involving 1723 patients with prostate cancer.

The FDA's Assessment:

As summarized in Applicant - Table 12: Efficacy Data for Prostate Carcinoma Patients Treated With Leuprolide Acetate 45 mg, 6-month Depot Formulations above, the Applicant identified published reports of five non-comparative, open-label studies which evaluated effects of two injections of 45 mg leuprolide acetate depot forms, and thus may be considered comparable to FP01C-13-001. Table 13 below summarizes verbatim the safety information provided in those five published repots. The information provided in these reports suggests that the major toxicities of comparable marketed leuprolide forms are related to androgen deprivation or to underlying prostate cancer.

Table 13. Safety Information in Published Trials of 6-Month Depot Leuprolide Products

Reference	Safety Findings (verbatim from published reports)
(Tunn, 2011; Ohlmann and Gross-Langenhoff, 2018)	"The local tolerability of the product was assessed as good or very good for most patients (92%). Adverse events (AEs) occurred in 108 (9%) of 1273 documented patients. Non-serious AEs were reported for 69 patients (5%) and serious adverse events (SAEs) were documented in 39 patients (3%). No systematic allergic reactions were reported for any patient. For 17 of 69 patients, a causal relationship between the occurrence of a non-serious AE and the administration of 6-monthly leuprolide acetate was excluded, whereas 34 patients had AEs which were assessed by the physicians as definitely related to treatment. A causality assessment was missing or was deemed not possible for 18 patients with non-serious AEs. Most reported SAEs were tumor progression (i.e., metastasis) or the requirement of surgical measures including radical prostatectomy, surgery and hospitalisation. Twenty-five patients (2%) died during the study. For 33 of 39 patients with SAEs, a causal relationship between the SAE and treatment with 6-monthly leuprolide acetate was excluded or assessed as being unlikely. For one SAE (tumor progression with fatal outcome) in an 82-year-old patient, a causal relationship to 6-monthly leuprolide acetate could not be excluded. A causality assessment was missing for 5 patients with SAEs."
(Shore et al., 2017)	"The safety profiles were similar between study cohorts and were as expected for treatment with an LHRH agonist. The most common adverse event (AE) was hot flashes and sweats (56–73% across every study), which is an expected pharmacological consequences of testosterone suppression. Pain at the injection site was reported in 2.3–4.6% of injections across studies. One treatment-related serious AE was reported in the 4-month formulation study (hospitalization for severe depression with suicidal ideation). No cardiovascular serious AE or other treatment-related serious AEs were reported across the four studies."
(Spitz et al., 2012; Spitz et al., 2016)	"Treatment-emergent AEs were reported for 94.7% of subjects during the treatment period; the majority of AEs were mild to moderate in severity. AEs ofinjection site reaction were reported in 37 subjects (24.5%), including injection site pain in 27 subjects (17.9%), injection site discomfort and injection site erythema each in 3 subjects (2.0%)

Reference	Safety Findings (verbatim from published reports)
	and injection site hematoma and injection site swelling in 2 subjects each (1.3%). All were mild or moderate in severity, and none led to discontinuation of study drug." "In addition to injection site pain, AEs of anemia, bone fracture, diabetes and cardiac events were of interest because of their possible association with androgen deprivation therapy. Ten subjects had AEs of anemia or decreased hemoglobin. Two of these AEs were considered serious, and the subjects received blood transfusions, but these events were considered not related to study drug by the investigator (alternative etiologies of suspected subacute upper gastrointestinal bleeding and metastatic cancer). Only 2 of the 10 AEs of anemia or decreased hemoglobin were considered treatment related. No subjects prematurely discontinued due to an AE of anemia. Five subjects experienced bone fractures as a result of falls or other trauma, but only one event was considered possibly related to study drug, and no subjects discontinued from the study due to an AE related to bone fractures. A total of eight subjects experienced AEs that were related to diabetes mellitus (n=2), increases in serum glucose (n=5) or hypoglycemia (n=1), which included one report of non-related new onset diabetes and only one possibly related event (increase in serum glucose)." "Overall, a high proportion of subjects (88.1%) had a history of cardiovascular disease. One or more cardiac events were reported for 18 subjects. Ten subjects experienced serious cardiac AEs, all of whom had medical histories with significant risk factors (for example, hypertension, coronary artery disease and hypercholesterolemia). One subject prematurely discontinued the study due to worsening coronary artery disease, weakness and hyperkalemia. A total of four treatment-related AEs were reported in three subjects: angina pectoris, tachycardia and mitral valve incompetence and tricuspid valve incompetence." "Overall, the incidence of sexual dysfunction during the study, reported as AEs, was low. One patient each reported reduced libido or loss of libido, and two patients reported erectile dysfunction." "Serious AEs were reported for 31 subjects (20.5%), including one death that was not considered related to study drug by the investigator. The subject was 92-years old, had a history of chronic obstructive pulmonary disease, and died as the result of a treatment-emergent AE of aspiration pneumonia that began 11 days after he completed the study. Two subjects had serious AEs that were considered possibly related to study drug: colonic pseudo-obstruction in one and angina pectoris in one. Both serious AEs resolved, and the subjects completed the study. Two subjects had serious AEs that resulted in discontinuation from the study: coronary artery disease, asthenia and hyperkalemia in one and non-Hodgkins lymphoma stage IV in one."
(Mostafa et al., 2014)	The publication did not discuss safety.
(Crawford et al., 2006)	"After baseline 82 participants had reported 211 treatment related adverse events, of which 210 were mild to moderate with 1 reported as severe. The most common treatment related adverse events, calculated as a percent of total participants, were hot flashes (mild in 33.3% and moderate in 24.3%), injection site burning (mild in 14.4% and

Reference	Safety Findings (verbatim from published reports)
	moderate in 0.9%), fatigue (mild in 7.2% and moderate in 4.5%), testicular atrophy (mild in 5.4%) and gynecomastia (mild in 3.6%). There were no clinically significant changes in vital signs."

8.2.1 Safety Review Approach

Data / The Applicant's Position:

Foresee provides a clinical safety database for Camcevi™ 42 mg consisting of the following information:

a. Safety and tolerability information from the main clinical Phase 3 12-month study and its 12-month safety extension in patients with prostate carcinoma in need for ADT (Studies FP01C-13-001, FP01C-13-001-EX; n = 137 patients treated with Camcevi™ 42 mg for up to 1 year, and n = 30 patients treated with Camcevi™ 42 mg for up to one additional year, amounting to 2 years total exposure). Changes in bone and urinary pain, urinary signs and symptoms, and assessment of local skin tolerability were of particular interest (Study FP01C-13-001);

b. Previous findings on safety and tolerability for comparable marketed leuprolide depot forms as laid down in product labeling

c. Supportive safety data from patients with prostate cancer treated with 6-month leuprorelin depot forms in published clinical studies (Crawford et al., 2006; Ohlmann and Gross-Langenhoff, 2018; Shore et al., 2017; Spitz et al., 2012; Spitz et al., 2016; Tunn, 2011). A thorough PubMed search was performed, and results obtained from the analysis of clinical safety information identified 5 safety studies involving 1723 patients with prostate cancer

d. A FAERS database search identifying adverse events in male patients where leuprolide products were listed as the primary suspect drug; the search will include 2017 Q1 through the most recently available quarter to capture adverse events that were not included in the most recent label updates (2019) for leuprolide products.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the safety database for this NDA.

8.2.2 Review of the Safety Database

Overall Exposure

Data / The Applicant's Position:

Out of 137 subjects in main clinical Study FP01C-13-001, 9 (6.6%) did not receive the second dose of Camcevi™ 42 mg. All other subjects received 2 doses. The mean study duration was 321.6 ± 54.4 days. In the safety extension Study FP01C-13-001-EX, 13 subjects (43.33%) did not receive the second dose of Camcevi™ 42 mg. All other subjects received 2 doses of Camcevi™ 42 mg. The mean study duration was 260.5 ± 97.4 days (refer to NDA Module 2.7.4, Section 2.7.4.1.2).

Of the 137 enrolled subjects in main clinical study, 15 (10.9%) subjects did not complete the study, including 5 subjects who terminated early due to adverse events (AEs) (Study FP01C-13-001). Of the 30 enrolled subjects in safety extension study, 5 (16.67%) subjects did not complete the study; early terminations due to AEs did not occur (Study FP01C-13-001-EX).

The FDA's Assessment:
The FDA agrees with the Applicant's summary of subjects' exposure to leuprolide injectable emulsion in the main study and the extension study.

Relevant characteristics of the safety population:

Data / The Applicant's Position:

The average age of the 137 subjects of Study FP01C-13-001 was 71.1 ± 8.7 years (mean ± SD), and all were male. Almost 90% of enrolled subjects were White (89.8%), followed by Black (5.8%), Asian (3.6%), and unknown (0.7%). The average duration with diagnosed prostate cancer was 4.9 ± 6.58 years. Approximately 50.4% of subjects had prostate carcinoma stage ≥ III, while approximately 25.5% of subjects had stage ≤ II. Regarding ECOG performance status, 83.2% of subjects were Grade 0 and 16.1% of subjects were Grade I (Study FP01C-13-001). Of the 30 subjects enrolled into the safety extension Study FP01C-13-001-EX, the average age was 75.0 ± 7.86 years. The average duration with diagnosed prostate carcinoma was 11.0 ± 7.21 years. More than 80% of subjects were White (25/30, 83.33%), followed by Black (3/30, 10%), Asian (1/30, 3.33%), and unknown (1/30, 3.33%). Regarding disease stage, 40% (12/30) of subjects had prostate carcinoma stage ≥ III, while 43.3% (13/30) subjects had prostate carcinoma stage ≤ II. Regarding ECOG performance status, 80% (24/30) of subjects had Grade 0, 6.67% (2/30) had Grade 1, and 3.33% (1/30) had Grade 2 (Study FP01C-13-001-EX).

Among the identified clinical studies using a 6-month leuprolide depot forms, all were conducted in an adult prostate cancer population in need for ADT (Crawford et al., 2006; Ohlmann and Gross-Langenhoff, 2018; Shore et al., 2017; Spitz et al., 2012; Spitz et al., 2016; Tunn, 2011). An exact number of geriatric subjects cannot be calculated, but all 5 studies were

conducted in adults with a mean age > 65 years old. In all, the study populations can be regarded as comparable (refer to NDA Module 2.7.4., Section 2.7.4.9, Table 14).

The FDA's Assessment:
The FDA agrees with the Applicant's characterization of the safety database and verified the values cited using submitted datasets.

Adequacy of the safety database:

Data / The Applicant's Position:

Camcevi™ 42 mg is being submitted in this NDA via the 505(b)(2) regulatory pathway.

The Sponsor established a scientific bridge to the approved Lupron® labeling through a demonstration of lower exposure to leuprolide from Camcevi™ 42 mg (Study FSEE-CSC-100) and intends to rely on the clinical and nonclinical safety of Lupron® (refer to NDA Module 2.5.1.)

The size of the safety database consisting of 137 subjects (Study FP01C-13-001 and Study FP01C-13-001-EX) is comparable to the size of study databases for similar follow-on depot formulations in published literature (Crawford et al., 2006).

The FDA's Assessment:
The FDA agrees that the safety database is adequate to support this 505(b)(2) NDA.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data / The Applicant's Position:

A total of 5 interim safety reviews were conducted during Study FP01C-13-001. The interim analyses were overseen by an Independent Data Monitoring Committee and an Independent Statistical Center.

In all, the data quality and integrity is considered appropriate and not compromised by the pre-specified interim analyses.

The FDA's Assessment:
The submission was well organized and complete, and the information presented was consistent between case report forms, datasets, clinical study reports, and narrative summaries

for individual patients. There is no evidene that the five interim safety reviews conducted compromised the quality or integrity of the data.

Categorization of Adverse Event

Data / The Applicant's Position:

All adverse events within the study period were captured and the severity of events was defined in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.3 to describe the maximum intensity of the adverse event. The verbatim adverse event (AE) terms were coded using the MedDRA dictionary, version 19.1, and classified by system organ class (SOC) and preferred terms (PTs) (Study FP01C-13-001; Study FP01C-13-001-EX).

The FDA's Assessment:
The NCI CTCAE and MedDRA are adverse event capturing and coding systems widely used by the Agency and the biopharmaceutical industry for regulatory purposes. Their use in this application is acceptable.

Routine Clinical Tests

Data / The Applicant's Position:

Safety analysis in this study was based on the safety information from the laboratory evaluations, AEs, and SAEs (Study FP01C-13-001, Study FP01C-13-001-EX, Section 12).

The results of the assessment by the clinical laboratory analysis (hematology, biochemistry, and urinalysis) are summarized in Section 12.4.2. of the CSR FP01C-13-001 and Section 12.4.2. of the CSR FP01C-13-001-EX.

The safety profile of Camcevi™ 42 mg was also assessed by physical examination (head, neck, heart, chest, lungs, abdomen, extremities, lymph nodes, musculoskeletal and neurological), including vital signs (systolic blood pressure, (SBP); diastolic blood pressure, (DBP); heart rate, respiratory rate, and body temperature) (Study FP01C-13-001, Section 12.5).

For summarized results refer to the FP01C-13-001 CSR.

For Study FP01C-13-001-EX the safety profile of Camcevi™ 42 mg was also assessed by physical examination (general appearance, skin, eyes, Ear/ Nose/ Throat (ENT), head, neck, heart, chest, lungs, abdomen, extremities, lymph nodes, musculoskeletal, and neurological), and vital signs

(systolic blood pressure, SBP; diastolic blood pressure, DBP; heart rate, respiratory rate, body temperature, and weight) (Study FP01C-13-001-EX, Section 12.5).

For summarized results refer to the FP01C-13-001-EX CSR.

The FDA's Assessment:
The schedule of assessments in FP01C-13-001 and FP01C-13-001-EX, in combination with publically available safety information for leuprolide acetate products, was adequate to characterize the safety of leuprolide injectable emulsion for patients with prostate cancer.

8.2.4 Safety Results

Deaths

Data / The Applicant's Position:

Sponsor-conducted Studies
In main Study FP01C-13-001, 3 deaths were reported. The causes of death included cerebrovascular accident, pulmonary embolism, and metastatic prostate cancer to lungs and acute kidney injury. All fatal events were determined to be unrelated to investigational product.

No deaths were reported in the safety extension Study FP01C-13-001-EX.

Published Literature
Two studies reported deaths during the treatment period. One death was a 92-year old subject with a history of chronic obstructive pulmonary disease, who died as a result of a treatment-emergent AE of aspiration pneumonia that began 11 days after he completed the study (Spitz et al., 2012). This was determined to be unrelated to study drug. An additional study reported 25 deaths during the study period; however, no further details were stated regarding the circumstances or relation to study drug (Tunn, 2011).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Section 6 of product labeling therefore states that "Fatal adverse reactions occurred in 2% of patients, including cerebrovascular accident (0.7%) and pulmonary embolism (0.7%)".

The incidence and causes of deaths reported in FP01C-13-001 were consistent with those expected in the patient population being studied and do not raise new safety concerns for leuprolide injectable emulsion.

Serious Adverse Events

Data / The Applicant's Position:

Sponsor-conducted Studies

There were 34 SAEs reported in 20 subjects in main Study FP01C-13-001. A list of SAEs by subject is presented in NDA Module 2.7.4., Section 2.7.4.2.1.3. A summary of SAEs by Preferred Term is provided in Applicant - Table 7. The most common (≥ 1%) SAE observed was subdural haematoma (1.5%). Of the 34 subjects, only 3 SAEs (1 per subjects) were determined to be related to the investigational product. These included blurred vision, left hip fracture, and myocardial infarction.

There were 7 new SAEs reported in 4 subjects in Study FP01C-13-001-EX. These SAEs by preferred term were deep vein thrombosis, dyspnoea, hip fracture, knee arthroplasty, perforated ulcer, pyelonephritis acute, and sepsis. All new SAEs were determined to be unrelated to the administration of Camcevi™ 42 mg by the investigators.

A summary of SAEs by Preferred Term, reported in both the main study and safety extension, is provided in Applicant - Table 7.

Applicant - Table 14: Summary of Incidence of Serious Adverse Events in the Main Study and Safety Extension

	Previous SAEs (N = 137)			New SAEs (N = 30)			Total SAEs (N = 137)		
	Event	Subject	(%)	Event	Subject	(%)	Event	Subject	(%)
OVERALL	34	20	(14.60%)	7	4	(13.33%)	41	22	(16.06%)
Subdural haematoma	2	2	(1.46%)	0	0	(0%)	2	2	(1.46%)
Acute respiratory failure	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Angina pectoris	2	1	(0.73%)	0	0	(0%)	2	1	(0.73%)
Asthenia	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Asthma	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Atrial fibrillation	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Bronchitis bacterial	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Cerebrovascular accident	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Chronic obstructive pulmonary disease	3	1	(0.73%)	0	0	(0%)	3	1	(0.73%)
Clostridium difficile colitis	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Colon adenoma	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Colon cancer	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)

	Previous SAEs (N = 137)			New SAEs (N = 30)			Total SAEs (N = 137)		
	Event	Subject	(%)	Event	Subject	(%)	Event	Subject	(%)
Death	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Deep vein thrombosis	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Dehydration	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Diabetic foot	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Dysphagia	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Dyspnoea	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Hip fracture	1	1	(0.73%)	1	1	(3.33%)	2	1	(0.73%)
Intermittent claudication	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Joint dislocation	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Knee arthroplasty	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Metabolic encephalopathy	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Myocardial infarction	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Non-cardiac chest pain	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Osteoarthritis	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Perforated ulcer	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Peripheral artery occlusion	2	1	(0.73%)	0	0	(0%)	2	1	(0.73%)
Pneumonia	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Pneumothorax spontaneous	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Prostate cancer metastatic	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Pyelonephritis acute	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Sepsis	0	0	(0%)	1	1	(3.33%)	1	1	(0.73%)
Vertigo	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)
Vision blurred	1	1	(0.73%)	0	0	(0%)	1	1	(0.73%)

Previous SAEs: The SAEs were captured from previous FP01C-13-001 study; New SAEs: The SAEs were captured from FP01C-13-001-EX study; Total SAEs: The combination of previous SAEs and New SAEs.

The N indicated the number of safety population, defined as subjects receiving at least one dose of LMIS 50 mg.

The MedDRA version was 20.1.

The AE percentage: 100%*the number of subjects with event (n) / Total number of subjects in Safety population (N)

For subject with the same AE but multiple different severity/relationship (which resolution date=onset date or resolution date=onset date+1, except they had different AE No.), the multiple events would be combined as one AE with the maximum severity/relationship category for analysis.

AE = adverse event; LMIS = leuprorelin mesilate injectable suspension; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

Source: Extension FP01C-13-001-EX, Table 12-16

Published Literature
Serious adverse events were assessed among 5 studies in 1723 patients with 6-month leuprolide acetate depot.

Pseudo-obstruction and angina pectoris were considered possibly related to the study drug; both resolved during the study (Spitz et al., 2012; Spitz et al., 2016). Ten patients experienced serious cardiac AEs, although these originated in patients who presented with medical histories with significant risk factors (eg, hypotension, hypertension, coronary artery disease, hypercholesterolemia) (Spitz et al., 2012; Spitz et al., 2016). Two subjects had anaemia that was considered serious; these subjects received blood transfusions and the events were considered not related to the study drug. Non-Hodgkins lymphoma stage IV was also reported in 1 patient (Spitz et al., 2012; Spitz et al., 2016). SAEs were documented in 39 patients (3% of study population) in another study, although most were tumour progression/metastasis or the requirement of surgical measures including radical prostatectomy, surgery, and hospitalization (Tunn, 2011; Ohlmann and Gross-Langenhoff, 2018). For 33 of these patients, study drug was deemed unlikely to be the cause. For 1 SAE in an 82-year-old patient (tumour progression with fatal outcome), a causal relationship to the drug could not be excluded. A causality assessment was missing for the remainder of patients with SAEs (Tunn, 2011; Ohlmann and Gross-Langenhoff, 2018).

The FDA's Assessment:
Known adverse effects of androgen deprivation include acceleration of atherosclerosis, prolongation of the QT interval, osteoporosis, hyperglycemia, anemia, cognitive decline, gynecomastia, hot flashes, and loss of libido. Many of these effects are nonspecific and common in aging individuals. The overall pattern of SAEs reported in FP01C-13-001 and FP01C-13-001-EX is consistent with that expected in men in the demographic group and the disease under study, and are consistent with toxicities reported in published clinical trials of leuprolide.

Section 6 of product labeling therefore includes the statement that "Serious adverse reactions occurred in 15% of patients who received CAMCEVI, including 1% of patients who experienced subdural hematoma".

Dropouts and/or Discontinuations Due to Adverse Effects

Data / The Applicant's Position:

Sponsor-conducted Studies
In main Study FP01C-13-001 (Section 12.3.1.3), there were 5 subjects (3.6%) who experienced AEs that led to premature discontinuation. This included 6 events: acute kidney injury, atrial

fibrillation, cerebrovascular accident, death, hormone-refractory prostate cancer, and prostate cancer metastatic. All events were determined to be unrelated to the investigational product.

In extension Study FP01C-13-001-EX (Section 12.3.2), no death or AE led to discontinuation.

Published Literature
Publications that presented data for 6-month leuprolide acetate depot formulations were identified and reviewed for potential safety findings.

AEs leading to discontinuation were reported in up to 3.4% of subjects in a single study. Reported AEs that led to discontinuation, regardless of relation to study drug, included coronary artery disease, asthenia, hyperkalaemia (Spitz et al., 2012; Spitz et al., 2016), disease progression, myocardial infarction, and stroke (Crawford et al., 2006; Shore et al., 2017). The designs of both studies that reported discontinuations dosed patients with 45 mg leuprolide for 6 months for a total of 2 doses.

The FDA's Assessment:
The FDA agrees that the reported AEs which led to study discontinuation were unlikely to have been caused by study drug and are consistent with those reported in published literature.

Dose Interruption/Reduction Due to Adverse Effects

Data / The Applicant's Position:
Not applicable.

The FDA's Assessment:
No dose reductions occurred during FP01C-13-001. Leuprolide injectable emulsion is a depot formulation, and the trial did not allow for the Day 168 dose of leuprolide injectable emulsion to be reduced in patients who experienced toxicity during the first 168 days.

Significant Adverse Events

Data / The Applicant's Position:

In main Study FP01C-13-001 (Section 12.3.1.3), there were 5 subjects (3.6%) who experienced AEs that led to premature discontinuation. This included 6 events: acute kidney injury, atrial fibrillation, cerebrovascular accident, death, hormone-refractory prostate cancer, and prostate cancer metastatic. All events were determined to be unrelated to the investigational product.

In extension Study FP01C-13-001-EX (Section 12.3.2), no death or AE led to discontinuation. All other significant AEs, including deep vein thrombosis, dyspnoea, hip fracture, knee arthroplasty, perforated ulcer, pyelonephritis acute, and sepsis (all 1 subject each) were unrelated to the administration of LMIS 50 mg.

The FDA's Assessment:
No adverse events that led to discontinuation of patients from FP01C-13-001 or FP01C-13-001-EX appeared to be probably or definitely related to study drug.

Treatment Emergent Adverse Events and Adverse Reactions

Data / The Applicant's Position:
Main Study FP01C-13-001
A total of 553 TEAEs from 114 subjects (83.2%) were reported with 144 TEAEs in 85 subjects (62.0%) reported as drug-related AEs in the main clinical Study FP01C 13 001. Most TEAEs were mild or moderate. There were 24 severe AEs in 18 subjects and 3 deaths occurred. There were 34 SAEs in 20 subjects (14.6%). APPEARS THIS WAY ON ORIGINAL
For a tabular summary refer to Study FP01C-13-001, Table 12-33.

The most common (≥ 5%) TEAEs observed were hot flush (48.9%), followed by hypertension (14.6%), pain in extremity (9.5%), injection site pain (7.3%), arthralgia (6.6%), fatigue (6.6%), nocturia (5.8%), back pain (5.1%), and nasopharyngitis (5.1%).

Most AEs were mild or moderate. The most common mild TEAEs (≥ 5%) were hot flush (46%), pain in extremity (7.3%), and arthralgia (6.6%). No TEAE with moderate severity ≥ 5% was reported in the present study. The severe AEs included atrial fibrillation, acute respiratory failure, asthma, chronic obstructive pulmonary disease, clostridium difficile colitis, colon adenoma, colon cancer, diabetic foot, hip fracture, intermittent claudication, joint dislocation, myocardial infarction, non-cardiac chest pain, osteoarthritis, peripheral artery occlusion, pneumothorax spontaneous, presyncope, prostatic specific antigen increased, road traffic accident, subdural hematoma, vertigo, and vision blurred, all occurring at a rate of 0.7% within the study population.

Of 137 subjects, 144 TEAEs in 85 subjects (62%) were determined to be drug-related AEs by investigators. The most common (≥ 5%) drug-related AEs were hot flush (48.2%), injection site pain (7.3%), and fatigue (5.8%). Most drug-related AEs were mild or moderate in severity. Only 3 severe drug-related AEs were observed during the study, including hip fracture (0.7%), myocardial infarction (0.7%), and vision blurred (0.7%).

Extension Study FP01C-13-001-EX

A total of 60 TEAEs were reported in 12 subjects (40%) during the extension Study FP01C-13-001-EX. Only 1 moderate TEAE from 1 subject (3.33%) was reported as a drug-related event. Most TEAEs were mild or moderate, with 8 severe AEs in 4 subjects and 3 life-threatening AEs in 2 subjects. However, the reported severe or life-threatening AEs were not related to LMIS 50 mg as determined by the investigators. There were no deaths reported in the extension study. There were 7 SAEs in 4 subjects [13.33%].

For a tabular summary refer to Study FP01C-13-001-EX, Table 12-8.

The most common (≥ 5%) new TEAEs were acute kidney injury, dehydration, increased blood triglycerides, dizziness, fall, fatigue, and hypertension (2 subjects each, 6.67%). The most common TEAEs for these same 30 subjects in the main study were hot flush (50%), pain in extremity (20%), arthralgia (16.67%), nasopharyngitis (16.67%), hypertension (13.33%), nocturia (13.33%), pneumonia (10%), sinusitis (10%), atrial fibrillation (6.67%), alanine aminotransferase increased (6.67%), aspartate aminotransferase increased (6.67%), blood alkaline phosphatase increased (6.67%), back pain (6.67%), confusional state (6.67%), contusion (6.67%), dizziness (6.67%), insomnia (6.67%), neck pain (6.67%), and upper respiratory tract infection (6.67%). Most of these TEAEs from the main study were resolved or the percentage of incidence was decreased to ≤ 5% in the extension study, except for hypertension and dizziness (extension Study FP01C-13-001-EX, Section 12.2.3).

Most new AEs were mild or moderate. New, severe AEs included acute kidney injury, atrioventricular block second degree, deep vein thrombosis, Escherichia sepsis, fall, hip fracture, knee arthroplasty, and ureterolithiasis (all 3.33%). Life-threatening AEs included perforated ulcer, pyelonephritis acute, and sepsis (all 3.3%).

Only 1 drug-related AE, neutropenia (3.33%), was reported. The severity of the AE was moderate.

In both the main Study FP01C-13-001 and the extension Study FP01C-13-001-EX, 114/137 subjects (83.21%) had at least 1 TEAE, totalling 613 TEAEs during both periods. Of these events, 145 TEAEs in 85 subjects (62.04%) were reported as drug-related. Seventy-five subjects (54.74%) had 116 mild drug-related TEAEs, 19 (13.87%) had 26 moderate drug-related TEAEs, and 3 (2.19%) had 3 severe drug-related TEAEs. Overall, 22 subjects (16.06%) had 41 SAEs during both study periods. The summary of AEs in both studies is presented in (Applicant - Table 8).

Applicant - Table 15: Summary of Treatment-emergent Adverse Events in Both Studies

	Previous TEAEs (N = 137)			New TEAEs (N = 30)			Total TEAEs (N = 137)		
Variables \ Status	**Event**	**Subject**	**(%)**	**Event**	**Subject**	**(%)**	**Event**	**Subject**	**(%)**
TEAEs									
Total	553	114	(83.21%)	60	12	(40%)	613	114	(83.21%)
TEAEs by severity									
Mild	395	105	(76.64%)	25	9	(30%)	420	106	(77.37%)
Moderate	130	59	(43.07%)	24	9	(30%)	154	66	(48.18%)
Severe	24	18	(13.14%)	8	4	(13.33%)	32	20	(14.60%)
Life-Threatening	0	0	(0%)	3	2	(6.67%)	3	2	(1.46%)
Death	4	3	(2.19%)	0	0	(0%)	4	3	(2.19%)
TEAEs by relationship									

Definite	56	39	(28.47%)	0	0	(0%)	56	39	(28.47%)
Possible	88	63	(45.99%)	1	1	(3.33%)	89	63	(45.99%)
Unrelated	409	95	(69.34%)	59	12	(40%)	468	96	(70.07%)
Drug-related AEs*									
Total	144	85	(62.04%)	1	1	(3.33%)	145	85	(62.04%)
Drug-related AEs* by severity									
Mild	116	75	(54.74%)	0	0	(0%)	116	75	(54.74%)
Moderate	25	18	(13.14%)	1	1	(3.33%)	26	19	(13.87%)
Severe	3	3	(2.19%)	0	0	(0%)	3	3	(2.19%)
SAEs									
Yes	34	20	(14.60%)	7	4	(13.33%)	41	22	(16.06%)

Previous TEAEs: The TEAEs were captured from previous FP01C-13-001 study; New TEAEs: The TEAEs were captured in this FP01C-13-001-EX study; Total TEAEs: The combination of previous TEAEs and New TEAEs.
The N indicated the number of safety population, defined as subjects receiving at least one dose of LMIS 50 mg.
The AE percentage: 100%*the number of subjects with event (n) / Total number of subjects in Safety population (N)
For subject with the same AE but multiple different severity/relationship (which resolution date=onset date or resolution date=onset date+1, except they had different AE No.), the multiple events would be combined as one AE with the maximum severity/relationship category for analysis.
*Causal relationship to study drug: AEs related to study drug include AEs classified as 'Possible', 'Probably', or 'Definite'. AEs not related to study drug include AEs that are 'None' or 'Improbable'.
AE = adverse event; LMIS = leuprorelin mesilate injectable suspension; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Source: Extension Study FP01C-13-001-EX, Table 12-8

The FDA's Assessment:

Table 16 below summarizes all-grade adverse reactions occurring in 5% of patients and Grade 3-4 adverse reactions occurring in 2% of patients. Because relatively few adverse reactions were reported in the extension phase of the trial, data from only the main phase of the trial were included in Section 6 of the package insert. Note that although patients with pyelonephritis may experience back pain, the review team felt that the Preferred term Back pain was more appropriate to combine with the term Musculoskeletal pain.

The US package insert will state in summary that the most common adverse reactions (>10%) occurring during a median follow-up duration of 336 days were hot flush, hypertension, injection site reactions, upper respiratory tract infections, musculoskeletal pain, fatigue, and pain in extremity.

Table 16. All-Grade Adverse Reactions Occurring in 5% of Patients and Grade 3-4 Adverse Reactions Occurring in 2% of Patients

Adverse Reaction	FP01C-13-001 (N = 137)		FP01C-13-001-EX (N = 30)		Total (N = 137)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Vascular disorders						
Hot flush[a]	50	0	0	0	50	0
Hypertension[b]	15	0	7	0	17	0
General disorders and administration site conditions						
Injection site reactions[c]	11	0	0	0	11	0
Fatigue[d]	10	0	7	0	12	0
Infections and infestations						
Upper respiratory tract infection[e]	11	0	0	0	15	0
Urinary tract infection[f]	4	0	3	3	5	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	0	0	0	10	0
Musculoskeletal pain[i]	11	0	0	0	11	0
Arthralgia	7	0	0	0	7	0
Renal and urinary disorders						
Micturition urgencyj	6	0	3	0	7	0
Nocturia	6	0	0	0	6	0
Hematuria	4	0	0	0	4	0
Acute kidney injury	2	0	7	3	4	0.7
Injury, poisoning and procedural complications						
Hip fracture	0.7	0.7	7	7	2	2
Nervous system disorders						
Dizziness[k]	5	0.7	2	0	7	0
Cardiac disorders						
Atrial fibrillation	4	0.7	0	0	4	0.7

[a] includes hot flush and flushing
[b] includes hypertension, essential hypertension, and blood pressure increased
[c] includes injection site pain, injection site erythema, injection site hemorrhage, injection site nodule, injection site paraesthesia, injection site pruritus, and injection site warmth
[d] includes fatigue and asthenia
[e] includes upper repiratory tract infection, bronchitis, bronchitis bacterial, sinusitis, and naspharyngitis
[f] includes urinary tract infection, cystitis, and pyelonephritis acute
[i] includes musculoskeletal pain, bone pain, and back pain
[j] includes micturition urgency and dysuria
[k] includes dizziness, dizziness postural, vertigo, and vertigo positional

Laboratory Findings

Data / The Applicant's Position:

Main Study

In main Study FP01C-13-001 (Section 12.4 of CSR), standard haematology parameters, standard biochemical parameters and Urinalysis were assessed.
Statistically significant changes from baseline ($p < 0.05$) were observed in certain parameters at different time points. For a list of the findings refer to Study FP01C-13-001 (Section 12.4 of CSR).

While statistically significant changes were observed in a number of haematological parameters, the changes were not clinically significant in the investigator's opinion.

Overall, statistically significant changes in biochemical parameters were observed during the study period, but most of these changes were not clinically significant and were possibly related to pre-existing conditions. A few abnormal changes were found to have clinical significance:

• One subject had an abnormally high potassium level on Day 168; however, this was determined to be a laboratory error and was normal upon repeated analysis.

• One subject had higher than normal ALP and blood glucose level on Day 168 before dosing and higher than normal ALP on Day 336. The blood glucose levels returned to normal by the end of the study, and the higher ALP levels may be attributed to the higher ALP levels at baseline.

• One subject had a higher than normal blood glucose level on Day 336, but the subject had an established diagnosis of diabetes mellitus prior to entering the study.

• One subject had a higher than normal triglyceride level on Day 336.

None of these clinically significant findings were found to be related to the dosing of LMIS 50 mg.

Overall, statistically significant changes in urine pH and specific gravity were observed during the study, but no clinical significance was associated with these changes. The clinically significant presence of erythrocytes, leukocytes, and proteins were observed in 3 subjects during the study, but these changes were determined to not be related to the administration of LMIS 50 mg by the investigator.

Extension Study

In extension Study FP01C-13-001-EX (Section 12.4 of CSR) standard haematology parameters, standard biochemical parameters and Urinalysis were assessed.

Statistically significant changes from baseline ($p < 0.05$) were observed in certain parameters at different time points. For a list of the findings refer to Study FP01C-13-001-EX (Section 12.4 of CSR).

One subject (3.70%) had lower than normal findings in neutrophil counts (18%, LNR: 36% to 74%) on Day 336 (V6/EOS). This event of neutropenia was clinically significant, and it was possibly related to the use of LMIS 50 mg.

In summary, statistically significant changes were observed in a number of haematological assessments, and one case was clinically significant. In the investigator's opinion, the rest of the changes were not clinically significant.

Overall, statistically significant changes in biochemical assessments were observed during the study period, and 2 subjects were found to have clinically significant changes. However, these were determined to not be related to the dosing of LMIS 50 mg. Other changes were not clinically significant and possibly related to pre-existing conditions.

Urinalysis during the study included pH, specific gravity, and the presences of leukocytes, erythrocytes, or protein. No statistically significant changes from baseline were observed in all parameters at any different time points.

Approved LD Labeling

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes (AbbVie Inc, 2018).

Alterations in blood glucose levels were observed in the Sponsor-conducted main study (FP01C-13-001, Section 12.4). There was an overall statistically significant increase at the end of dosing periods during the main study. Three subjects had clinically significant increases in blood glucose levels: 2 in the main study and 1 in the safety extension. One normalized by the end of the study and the other subjects had preexisting conditions (diabetes and hypercholesterolemia). These results indicate that this statement in the LD label is also relevant for LMIS 50 mg.

Published Literature

Anaemia AEs were considered of interest because of their possible association with androgen deprivation therapy. Ten subjects (out of 151 subjects) had AEs of anaemia or decreased haemoglobin; two were considered serious, and the subjects received blood transfusions. However, only 2 of these anaemia AEs were considered treatment-related (Spitz et al., 2012). Mean haemoglobin values also decreased (mean change of -1.05 ± 1.01 g/dL) through the first 14 weeks of the 48-week treatment before stabilizing for the remainder of the treatment period (Spitz et al., 2012). While no cases of anaemia were reported in Study FP01C-13-001, a mean haemoglobin change of -0.82±0.949 g/dL was observed at the end of the dosing periods.

Out of 151 subjects, a total of 8 experienced AEs that were related to diabetes mellitus (n = 2), increases in serum glucose (n = 5), or hypoglycaemia (n = 1), which included 1 report of non-related new onset diabetes and only 1 possibly study drug-related event (increase in serum glucose). At baseline, the mean fasting blood glucose concentration was above normal (5.8 mmol/L) and further increased by 0.4 ± 1.8 mmol/L at the final treatment visit. However,

only 1 subject, who had a history of diabetes, had a glucose value that was considered potentially clinically significant (≥ 16.6 mmol/L) during the treatment period (Spitz et al., 2012). These results are similar to what was observed in the Sponsor-conducted main Study FP01C-13-001.

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or HgbA1c periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycaemia or diabetes. Alterations in blood glucose levels were observed in the Sponsor-conducted main Study FP01C-13-001 (Section 12.4 of CSR). There was an overall statistically significant increase at the end of dosing periods during the main study. Three subjects had clinically significant increases in blood glucose levels: 2 in the main study and 1 in the safety extension. One normalized by the end of the study and the other subjects had pre-existing conditions (diabetes and hypercholesterolemia).

The FDA's Assessment:
A total of nine Grade 3-4 laboratory abnormalities were reported in FP01C-13-001 (refer to Table 17 below). All were Grade 3, and consisted of anemia (n = 4), hyperglycemia (n = 4), and hypophosphatemia (n = 1). No SAEs pertaining to laboratory abnormalities were reported during the trial.

Hyperglycemia is a known adverse effects of ADT and is included as a Warning and Precaution in section 5. Overall, a table of laboratory abnormalities was not added to Section 6 as most were infrequent and/or felt to be clinically unimportant.

Vital Signs

Data / The Applicant's Position:

In main Study FP01C-13-001 (Section 12.5 of CSR), the safety profile of Camcevi™ 42 mg was further assessed by physical examination (head, neck, heart, chest, lungs, abdomen, extremities, lymph nodes, musculoskeletal, and neurological), including vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, respiratory rate, and body temperature).

No statistically significant change was observed for vital signs. A statistically significant increase in body weight (kg; 1.839 ± 4.3143, $p < 0.001$) was observed on Day 336 (V23/EOS).

Physical examination results were normal in most subjects during the study. Results of physical examination revealed that most subjects were normal in head, neck, and lymph nodes assessment, while 1 subject each in heart and lung had abnormal findings, 5 subjects each had

abnormal findings in chest and abdomen, 7 subjects had abnormal findings in extremities, 2 subjects had abnormal findings in musculoskeletal, and 3 subjects had abnormal findings in neurological assessment at screening (V1). A total of 24 abnormal findings in physical exams were reported at screening (V1). On Day 168 (V14/EOT), while most subjects were assessed as normal, 1 subject each was reported with abnormal findings in head, neck, heart, and neurological exams; 2 subjects each were reported with abnormal findings in lungs and musculoskeletal exams, 5 subjects with abnormal findings in chest exams, 6 subjects with abnormal findings in abdomen, and 8 subjects with abnormal findings in extremities. A total of 27 abnormal findings were reported on Day 168 (V14/EOT). On Day 336(V23/EOS), while most subjects were assessed as normal, 1 subject each was reported to have abnormal findings in head, heart, and neurological exams; 2 subjects had abnormal findings in lungs; 5 subjects each had abnormal findings in chest and musculoskeletal exams; and 12 subjects had abnormal findings in extremities. A total of 36 abnormal findings were reported on Day 336 (V23/EOS).

In extension Study FP01C-13-001-EX (Section 12.5 of CSR), a physical examination (general appearance, skin, eyes, ears/nose/throat, head, neck, heart, chest, lung, abdomen, extremities, lymph nodes, musculoskeletal, and neurological) and vital signs (SBP, DBP, heart rate, respiratory rate, body temperature, and weight) were assessed.

No statistically significant change was observed for vital signs except a statistically significant decrease in mean body temperature (-0.19 ± 0.402°C; p = 0.0195) was observed on Day 336 (V6/EOS).

Results of physical examination revealed that most subjects were normal in assessment except for 10 subjects with abnormal findings at the screening visit (V1), including 4 subjects with abnormal findings in chest (mild gynecomastia), 2 subjects each with abnormal findings in skin and musculoskeletal exam, and 1 subject each with abnormal findings in abdomen, eyes, extremities, and neurological exams. On Day 168 (V4), 2 subjects each were reported with abnormal findings in skin and extremities, 1 subject each had abnormal findings in abdomen, chest, eyes, and neurological exam. A total of 8 abnormal findings were reported at this visit; the rest of the subjects were assessed as normal. On Day 336 (V6/EOS), while most subjects were assessed as normal, 9 abnormal findings were reported. Four subjects had abnormal findings in chest exams, 2 subjects had abnormal findings in skin, and 1 subject each had abnormal findings in eyes, extremities, and neurological exam. None of these abnormalities were judged to be of clinical significance.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. No significant changes in the mean value for any vital sign was observed among the 137 patients in FP01C-13-001 over time, and no patient experienced an abnormal value for any vital sign that was otherwise unexplained and/or assoiciated with clinical sequelae.

Electrocardiograms (ECGs)

Data / The Applicant's Position:

Cardiovascular function was also assessed by 12-lead electrocardiogram (ECG) in main Study FP01C-13-001 (Section 12.5, page 200 of CSR). Some changes in ECG were statistically significant when compared to the baseline values:

- the increase of heart rate (HR) 4 hr post-dosing on Day 0 (V2, 1.5 ± 8.01 bpm, p = 0.0135),
- the increase of HR 4 hr post-dosing on Day 168 (V14/EOT, 2.5 ± 10.13 bpm, p = 0.0057),
- the decrease of respiratory rate (RR) 4 hr post-dosing on Day 0 (V2, -24.525 ± 106.0359 ms, p = 0.0036),
- the decrease of RR 4 hr post-dosing on Day 168 (V14/EOT, -40.45 ± 136.524 ms, p = 0.0011),
- the decrease of QT duration 4 hr post-dosing on Day 0 (V2, -6.4 ± 28.18 ms, p = 0.0016),
- the increase of QT duration before dosing on Day 168 (V14/EOT, 8.4 ± 33.61 ms, p < 0.001),
- the increase of QT duration 4 hr post-dosing on Day 168 (V14/EOT, 6.0 ± 33.93 ms, p = 0.0106),
- the increase of QT duration on Day 336 (V23/EOS, 9.7 ± 39.07 ms, p < 0.001).

Sixty-six subjects (48.9%) were reported with abnormal but not clinically significant findings at baseline (Day 0, V2, 4 h post-dosing). On Day 168, before dosing with LMIS 50 mg, 51 subjects (40.2%) were reported to have abnormal but not clinically significant findings, while 1 subject (0.8%) had abnormal and clinically significant findings for the overall ECG interpretation. Four hours post-LMIS 50 mg dosing on Day 168 (V14/EOT), 56 subjects (44.1%) were reported with abnormal but not clinically significant findings, and no subjects were reported with abnormal but clinically significant findings for the overall ECG interpretation.

On Day 336 (V23/EOS), the number of subjects with abnormal but not clinically significant findings was 52 (9.7%) and 1 subject (0.8%) was reported with abnormal and clinically significant findings for the overall ECG interpretation. Two subjects had clinically significant abnormalities for overall interpretation on Day 336 (V23/EOS), including subject (b) (6) with atrial fibrillation on Day 168 (V14/EOT) before dosing, and subject (b) (6) with sinus bradycardia.

One patient discontinued from the study due to atrial fibrillation (moderate severity). The subject had a normal ECG at baseline, which then presented with premature atrial complex before the first dose administration. Four hours after the first dose, the ECG recording was sinus bradycardia with sinus arrhythmia 4 hours post-dosing and again at Visit 9. These were not judged to be clinically significant until Visit 14 before the second dosing of

Camcevi™ 42 mg. Although judged to not be related to the study drug, the patient was not given the second dose and was subsequently withdrawn from the study.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. The changes in HR, RR, and QT duration noted above were not assessed as clinically significant.

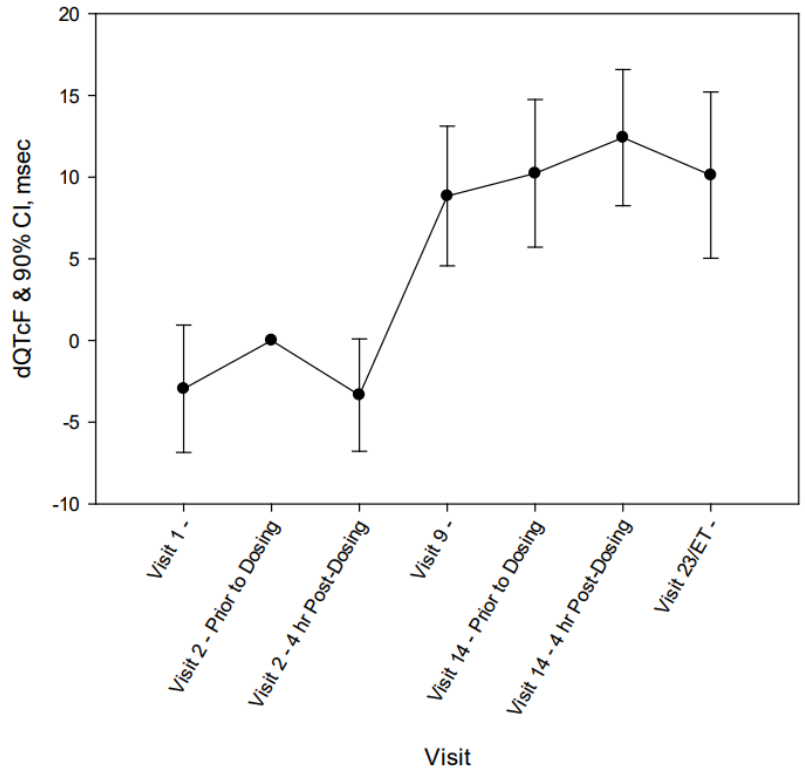
The incidence of clinically significant ECG events (1 [0.7%] patient discontinuing the study because of atrial fibrillation) is within the expected range for this patient population.

QT

Data / The Applicant's Position:

Post hoc analysis of ECG and plasma concentration was performed (main study FP01C-13-001, ecg-rep), because some subjects had high QTcF and dQTcF values during the study period. This analysis showed an increase in QTcF related to leuprorelin treatment. Mean change from baseline of QTcF at each time point is displayed in (Applicant - Figure 6). Minimal fluctuations were observed through 4 hours post-dosing, but by Day 28 (Visit 9) QTcF had increased 8.8 ms (90% CI 5.02, 12.7 ms) over baseline. Similar increases were noted pre- and post-dosing at Day 168 (Visit 14) and Day 336 (Visit 23), with the greatest change occurring post-dosing on Day 168 (12.4 ms [90% CI 8.44, 16.40 ms]).

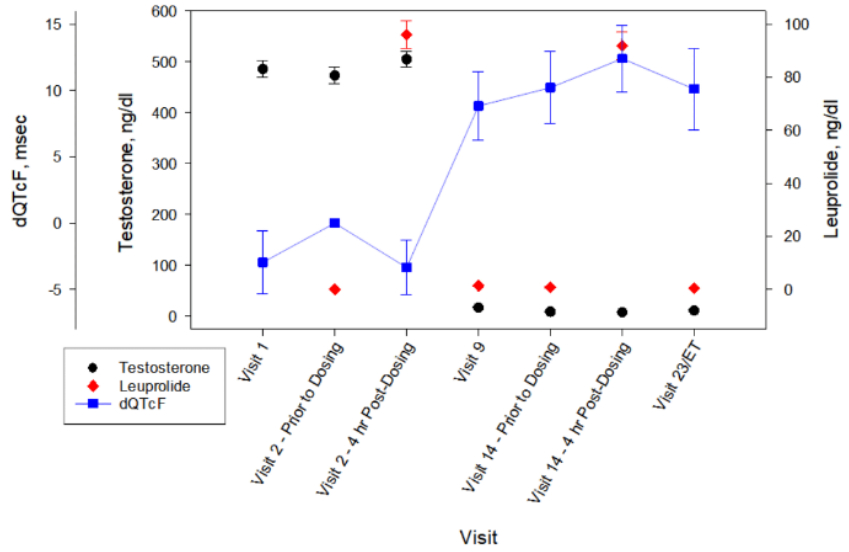
Applicant - Figure 8: Change in QTcF by Visit



Source: Main Study FP01C-13-001 Appendix 16-5 Figure 2

In Applicant - Figure 7, the change in QTcF is plotted with leuprolide and testosterone plasma concentrations. Central tendency analysis and concentration-effect modelling indicate that the increase in QTcF was not related to leuprolide itself. The observed increase does correlate well with the reduced testosterone plasma concentration induced by leuprolide. The mean increase in dQTcF exceeded 10 ms at the 4 ECG sampling time points from Day 28 through Day 336, and the upper boundary of the confidence interval in the concentration-effect model exceeded 10 ms at testosterone levels below 35 ng/dl.

Applicant - Figure 9: Plasma Concentrations and Changes in QTcF



Change in QTcF is plotted ± standard error
Source: Main Study FP01C-13-001 Appendix 16-5 Figure 3

Overall, 9 subjects had 15 outlier QTcF responses: QTcF ≥ 500 ms, or QTcF ≥ 480 ms with dQTcF ≥ 60 ms, or both. In 9 of these 15 events, alternate explanations for QT prolongation included prolonged QT event present at screening or baseline, newly added QT-prolonging drug, and ventricular pacing. Therefore, leuprolide treatment was the probable cause of QT prolongation in only 5 subjects (3.6% of all patients) for 6 events (0.64% of all time points). No adverse consequences were observed in association with these categorical responses.

In the extension Study FP01C-13-001-EX (Section 12.5, page 118 of CSR), 25 subjects (86.21%) were reported with abnormal but not clinically significant findings in ECG assessments at screening. On Day 168 (V4), 16 subjects (88.89%) were reported to have abnormal but not clinically significant findings. On Day 336 (V6/EOS), the number of subjects with abnormal but not clinically significant findings was 20 (74.07%) for the overall ECG interpretation. However, no clinically significant abnormalities were noted for the overall interpretation of 12-lead ECG assessments in this study.

The FDA's Assessment:
In 2013, the CDER QT Interdisciplinary Review Team reviewed QTc data for leuprolide. The review found a mean change from baseline of approximately 12 ms between Days 84 and 364. The review concluded, "We cannot be certain whether the QT prolongation is directly associated wth the plasma testosterone suppression alone or due to direct effects of leuprolide based on current data, although the former is quite plausible."

In 2014, the FDA Division of Pharmacovigilance II conducted a postmarketing safety review of GnRH analogue associated QT prolongation in men with prostate cancer. This review identified three postmarketing reports of GnRH analogue associated QT prolongation. Two reports occurred in patients receiving leuprolide, and one occurred in a patient receiving goserelin. All patients had confounding risk factors such as advanced age, structural heart disease, or a concomitant medication associated with QT prolongation; however, an association between GnRH analogues in men with prostate cancer and QT prolongation could not be ruled out. The literature review identified two clinical trials describing a QT prolonging effect which appeared to be due to androgen deprivation rather than a direct effect of leuprolide on cardiac myocyte repolarization.

(b) (5)

The Lupron Prescribing Information now contains the following Warning and Precautions regarding the effect on QT/QTc interval:

Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

The increase is QT/QTc interval observed during FP01C-13-001 is consistent with the effect described in published literature and in the package insert for Camcevi.

Immunogenicity

Data / The Applicant's Position:

No immunogenicity studies were considered necessary and have not been conducted.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. No carcinogenicity studies were conducted with leuprolide mesylate or LMIS. The Applicant is relying on findings from Lupron Injection 1 mg (NDA 019010) for this NDA submitted via the 505(b)(2) regulatory pathway

8.2.5 Analysis of Submission-Specific Safety Issues

Data / The Applicant's Position:

8.2.5.1 Local skin tolerability

The effect of administering Camcevi™ 42 mg was assessed by local skin tolerability in main Study FP01C-13-001 (Section 12.5, page 212 of CSR). The local skin tolerability was assessed in 4 aspects: itchiness sensation, erythema sensation, burning sensation, and stinging sensation. Of the 137 subjects administered Camcevi™ 42 mg, most subjects had no to mild skin irritation after the injection. Several subjects had moderate skin intolerances, including 7 subjects who were reported with local skin intolerance: 1 subject had moderate itching sensation, 3 subjects had moderate erythema sensation, 3 subjects had moderate burning sensation, and 2 subjects had stinging sensation with 1 being mild and 1 being moderate intensity.

Taken together, all the reported local skin reactions were mild or moderate in degree and were resolved by the end of study. These results suggest that Camcevi™ 42 mg did not cause any severe or permanent local skin intolerance.

8.2.5.2 Bone pain, urinary pain and urinary signs and symptoms

Change in bone pain and urinary pain (by VAS scale; 0 indicating no pain and 10 indicating worst pain ever) and the change in urinary signs and symptoms were assessed in main Study FP01C-13-001 (Section 12.5, page 215 of CSR).

The average degree of bone pain assessed was 0.72 ± 1.641 at baseline (Day 0, V2), 0.71 ± 1.773 on Day 168 (V14/EOT), and 0.97 ± 1.965 on Day 336 (V23/EOS). The average change in degree of bone pain was 0.07 ± 1.666 on Day 168 (V14/EOT) and 0.24 ± 1.988 on Day 336 (V23/EOS). The average degree of urinary pain was 0.35 ± 0.823 at baseline (Day 0, V2), 0.29 ± 0.782 on Day 168 (V14/EOT), and 0.44 ± 1.212 on Day 336 (V23/EOS). The average change in degree of urinary pain was -0.07 ± 0.847 on Day 168 (V14/EOT) and 0.09 ± 1.280 on Day 336 (V23/EOS). Taken together, no statistically significant change was observed in the bone pain or urinary pain assessments from Day 0 (V2) to Day 168 (V14/EOT) or from Day 0 (V2) to Day 336 (V23/EOS). These results suggest that the administration of Camcevi™ 42 mg did not cause additional bone or urinary pain in these subjects.

The degree of urinary signs and symptoms was assessed by a questionnaire consisting of 6 questions on urinary signs and 1 question on urinary symptoms:

Q1: Over the past month, how often have you had the sensation of not emptying your bladder completely after you finished urinating?

Q2: During the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

Q3: During the past month, how often have you found you stopped and started again several times when you urinate?

Q4: During the past month, how often have you found it difficult to postpone urination?

Q5: During the past month, how often have you had a weak urinary stream?

Q6: During the past month, how often have you had to push or strain to begin urination?

Q7: Over the past month, how many times did you most typically get up to urinate during the night?

The 6 questions were scaled from 0 to 5, with 0 indicating no symptom at all, 1 indicating less than 1 out of 5 times, 2 indicating less than half the time, 3 indicating about half of the time, 4 indicating more than half of the time, and 5 indicating almost always with symptom. Most (> 50%) subjects had none or less than 1 in 5 times for urinary signs and symptoms in response to questions 1 to 6 on Day 0 (V2), Day 168 (V14/EOT), and Day 336 (V23/EOS).

With regard to the frequency of urinating during the night (Q7), 37.2% of subjects had to urinate 0 to 1 time during the night while 62.8% of subjects had to urinate more than twice (inclusive) during the night on Day 0 (V2). On Day 168 (V14/EOT), 33.4% subjects had to urinate 0 to 1 time during the night, while 66.7% subjects had to urinate more than twice (inclusive) during the night. On Day 336 (V23/EOS), 32.6% subjects had to urinate 0 to 1 time during the night, while 67.4% subjects had to urinate more than twice (inclusive) during the night. Overall, these results suggested that the administration of Camcevi™ 42 mg did not change the urinary signs and symptoms in subjects with prostate cancer during the study period.

8.2.5.3 Hip fracture

Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with GnRH agonists. Anti-androgen therapy significantly increases the risk for fractures owing to osteoporosis. Only limited data is available on this issue. Fractures owing to osteoporosis were observed in 5% of patients following 22 months of pharmacological androgen deprivation therapy and in 4% of patients following 5 to 10 years of treatment. The risk for fractures owing to osteoporosis is generally higher than the risk for pathological fractures. Apart from long lasting testosterone deficiency, increased age, smoking and consumption of alcoholic beverages, obesity and insufficient exercise may have an influence on the development of osteoporosis.

The most common TEAEs (≥ 5%) in both studies combined were hot flush (48.91%), hypertension (16.06%), pain in extremity (9.49%), fatigue (8.03%), injection site pain (7.30%) arthralgia (6.57%), nocturia (5.84%), back pain (5.11%), and nasopharyngitis (5.11%). A total of 145 TEAEs in 85 subjects were determined to be drug-related by investigators. The most common were hot flush (48.18%), injection site pain (7.30%), and fatigue (5.84%) (Studies FP01C-13-001, FP01C-13 001-EX).

All combined moderate and severe TEAEs were ≤ 5%. The most common severe TEAE by preferred term was infection and infestations (1.46%) in 2 subjects during the whole study period. Combined, all life-threatening TEAEs were ≤ 5%; none occurred in the main study. Most drug-related AEs were mild or moderate in severity. Three severe drug-related AEs were

observed during the whole study period and occurred only in the main study: hip fracture, myocardial infarction, and vision blurred.

The FDA's Assessment:
In Section 6 *Adverse Reactions* of the Camcevi Prescribing Information, the FDA combined the Preferred terms Injection site pain, Injection site erythema, Injection site hemorrhage, Injection site nodule, Injection site paraesthesia, Injection site pruritus, and Injection site warmth for an 11% incidence of injection site reactions. The FDA also combined the Preferred terms musculoskeletal pain, bone pain, and back pain for an 11% incidence of musculoskeletal pain. A total of three hip fractures were reported, two of which occurred among the 30 patients in the extension study PR01C-13-001. The higher incidence of hip fractures during the extension part of the trial compared to during the first 48 weeks of treatment is not surprising, as hip fractures are thought to result from secondary osteoporosis or from progression of prostate cancer rather than a direct effect of leuprolide on bone.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data / The Applicant's Position:

The safety profile of leuprolide is well characterized in three decades of clinical use. Non-clinical studies with leuprolide mesylate demonstrated similar non-clinical safety characteristics as compared to leuprolide acetate.

Safety and tolerability information for Camcevi™ 42 mg has been obtained in the main clinical Phase 3 12-month study and its 12-month safety extension in patients with prostate carcinoma in need for ADT (Studies FP01C-13-001, FP01C-13-001-EX; n = 137 patients treated with Camcevi™ 42 mg for up to 1 year, and n = 30 patients treated with Camcevi™ 42 mg for up to one additional year, amounting to 2 years total exposure). Changes in bone and urinary pain, and urinary signs and symptoms, indicative of androgen flares or disease progression, as well local skin tolerability were of particular interest. The investigated population is deemed appropriate.

Of 137 subjects in main study FP01C-13-001, 144 AEs in 85 subjects (62%) were determined to be causally drug-related AEs by investigators. The most common (≥ 5%) drug-related AEs were hot flush (48.2%), injection site pain (7.3%), and fatigue (5.8%). Most drug-related AEs were mild or moderate in severity. Only 3 severe drug-related AEs were observed during the study, including hip fracture (0.7%), myocardial infarction (0.7%), and vision blurred (0.7%). The most common were hot flush (48.2%), injection site pain (7.3%), and fatigue (5.8%). Most drug-related AEs were mild or moderate in severity. In study extension FP01C-13-001-EX, the only drug-related AE was moderate neutropenia (3.3%).

Three deaths were reported (cerebrovascular accident, pulmonary embolism, and metastatic prostate cancer to lungs and acute kidney injury), which were all assessed to be unrelated to Camcevi™ 42 mg. Three SAEs (1 per subject) were determined to be causally related to Camcevi™ 42 mg: blurred vision, left hip fracture, and myocardial infarction.

The reported profile of drug-related AEs with Camcevi™ 42 mg is well in line with the adverse drug reaction (ADR) profile of comparable leuprolide depot products. This applies also to laboratory evaluation outcomes, ECG findings, AEs of special interest (bone and urinary pain, urinary signs and symptoms), and local skin tolerance.

Across Sponsor-conducted studies, no new AEs were identified for Camcevi™ 42 mg compared to previously-approved leuprolide products. The most common AEs were hot flush, hypertension, pain in extremity, fatigue, injection pain, arthralgia, nocturia, back pain, and nasopharyngitis; these are in line with safety issues identified in the approved labeling for Lupron® and AEs reported in the published literature. ECG recordings identified clinically significant QT prolongation in 5 subjects due to leuprolide treatment. However, this is a known risk for currently marketed leuprolide products (AbbVie Inc, 2018).

Camcevi™ 42 mg proved to be safe and well tolerated in the clinical studies, raising no specific safety or tolerability concern. Although the overall exposure to Camcevi™ 42 mg is comparably low, the PK/PD cross-study comparison exercises are deemed appropriate for bridging to the leuprorelin acetate safety database.

The nature of the AEs reported in the Sponsor's studies were consistent with those reported for the LD, Lupron®, and in the published literature for subjects treated with 6-month leuprolide depot formulations. Overall, the Sponsor has demonstrated that Camcevi™ 42 mg is generally well-tolerated and effective in suppressing testosterone levels for the treatment of prostate cancer (refer to NDA Module 2.5, Section 2.5.6.4).

The FDA's Assessment:
Formal clinical outcome assessments were not done as part of FP01C-13-001 or FP01C-13-001-EX.

8.2.7 Safety Analyses by Demographic Subgroups

Data / The Applicant's Position:

No pre-specified special safety analyses by demographic subgroups have been conducted on Camcevi™ 42 mg.

The FDA's Assessment:
Because prostate cancer occurs only in men, FP01C-13-001 enrolled only male patients. Because the overall sample size was small and most patients were older (median age was 74

years), White (76%), and non-Hispanic (91%), safety analyses by demographic subgroups of age, race, and ethnicity were not performed.

8.2.8 Specific Safety Studies/Clinical Trials

Data / The Applicant's Position:
User Risk Related Analysis (URRA)

A User Risk Related Analysis (URRA) was submitted to the Agency on 24 January 2019 under IND 103206, and is also resubmitted with this NDA. The URRA demonstrated that the device is safe in its operation, and accordingly has been used in the medical marketplace for many years. This request for comments and advice has not been reviewed by the FDA at the time of NDA submission (refer to NDA Module3.2.R.1.P.3 for device information).

Human Factors Studies are likely unnecessary when the following statements are true in accordance with *Applying Human Factors and Usability Engineering to Medical Devices:* Guidance for Industry and Food and Drug Administration Staff:

- The device design does not contain novel features:
  - The LMIS device does not contain novel features;
- The device has precedence in a healthcare environment:
  - The LMIS device design has been used for many years.;
- The device will be used exclusively by Healthcare Providers (HCPs)
  - The LMIS device will be used in a clinician's office, exclusively by appropriate, licensed healthcare provider under the supervision of appropriate clinic personnel.

Piston syringes, with compatible needles, have been cleared medical devices for well over 30 years, and medical professionals are accustomed to their use in the normal care of patients. Pre-filled, fixed-dose syringes additionally minimize dosing errors and decrease time for user adoption as typical variables, including reconstitution and drawing up the correct amount of drug, are not factors to administration. The product prescribing information will also include administration steps outlining information to ensure successful use of the product.

Based on the aforementioned information, our conclusion is that this device delivery mode is safe and well-understood by learned intermediaries and should not require a Human Factors Study.

The FDA agreed to the Applicant's position stating that based on its review of the URRA and comparative analyses, a human factors validation study is not required in support of your proposed leuprolide mesylate injectable suspension product. This was communicated to the Applicant in a post-meeting comment following a Type A meeting held 29 July 2019.

The FDA's Assessment:
The FDA agres with the Applicant's assessment.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data / The Applicant's Position:

Not applicable.

Please refer to Section 5.5.3 in the Nonclinical Pharmacology/Toxicology Section.

The FDA's Assessment:

No carcinogenicity studies were conducted with leuprolide mesylate or leuprolide injectable emulsion 50 mg. This NDA was submitted via the 505(b)(2) regulatory pathway, with Lupron Injection 1 mg as reference listed drug (NDA 019010). The Applicant established a scientific bridge to Lupron labeling through a demonstration of lower exposure to leuprolide from leuprolide injectable emulsion 50 mg (Study FSEE-CSC-100).

Human Reproduction and Pregnancy

Data / The Applicant's Position:

Pregnancy

Based on findings in animal studies and mechanism of action, leuprolide may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies, administration of a monthly formulation of leuprolide acetate on day 6 of pregnancy (sustained exposure was expected throughout the period of organogenesis) caused adverse embryo-fetal toxicity in animals at doses less than the human dose based on body surface area using an estimated daily dose. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus (AbbVie Inc, 2018).

Lactation

There is no information regarding the presence of leuprolide in human milk, the effects on the breastfed child, or the effects on milk production (AbbVie Inc, 2018).

Females and Males of Reproductive Potential

Preclinical studies with leuprolide, revealed in both sexes effects on the reproductive system, which were expected from the known pharmacological properties. These effects were shown to be reversible after discontinuation of the treatment and an appropriate period of regeneration.

Based on findings in animals and mechanism of action, leuprolide may impair fertility in males of reproductive potential.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The Camcevi Prescribing Information will

inform providers of these risks in males and females of reproductive potential as a Warning and Precaution in Section 5 of the package insert.

APPEARS THIS WAY ON ORIGINAL

Pediatrics and Assessment of Effects on Growth
Data / The Applicant's Position:

No investigations have been conducted with Camcevi™ 42 mg in paediatric populations. As the drug intended for use in prostate cancer, Camcevi™ 42 mg is not indicated for use in children.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Another leuprolide product Lupron Depot-Ped is approved for children with central precocious puberty.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data / The Applicant's Position:

Overdose

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose (AbbVie Inc, 2018).

As Camcevi™ 42 mg will only be administered under the supervision of a physician, providing quick access to medical care in the event of an overdose is not considered a significant concern. (2.7.4.5.5. NDA)

Drug Abuse

Camcevi™ 42 mg for the treatment of patients with prostate cancer will be administered under the supervision of a physician; patients will not have access to Camcevi™ 42 mg in an at-home setting. Therefore, the potential for abuse of Camcevi™ 42 mg is negligible.

Withdrawal and Rebound

After cessation of leuprolide, testosterone levels gradually rise after a certain period of time.

The FDA's Assessment:
On March 15, 2021, because of concern about the proposed upper range of the geometric mean $AUC_{0\text{-}24h}$ of Camcevi, the FDA Office of Pharmaceutical Quality asked the Applicant to submit details of any available clinical reports they might have of overdose for FDA review. On March 23, 2021, the Applicant queried FDA's Adverse Event Reporting System (FAERS) Public Dashboard for Individual Case Safety Reports (ICSRs) and the Eudra Vigilance Data Analysis System (EVDAS) associated with leuprolide and reporting as adverse events any of the MedDRA Preferred terms Overdose, Accidental overdose, Intentional Overdose or Prescribed overdose.

The following summarizes the Applicant's reported findings from these searches.

FAERS Public Dashboard Query

The FAERS query retrieved a total of 50,944 ICSRs relating to leuprolide, with the earliest cases received in 1984. Of these, 75 cases reported one of the Preferred terms of interest. Forty-eight of the 75 overdose cases (64%) were reported by healthcare professionals and 21 cases (28%) by consumers (report type not specified in 6 cases). Countries reporting 3 or more cases included the United States (40 cases; 53%), Canada (7 cases; 9%), Japan (5 cases; 7%) and France (3 cases; 4%). The overdose cases were received between 1997 and 2020 with no noteworthy time trend or pattern. Of the 75 cases, 45 (60%) were serious, including 6 cases (8%) reporting a fatal outcome. The indication for use of leuprolide was reported in 58 cases and included prostate cancer (32 cases), endometriosis (15 cases), other gynecological indications (8 cases) and precocious puberty (3 cases). Consistent with the demographic profile of the approved indications, most cases describe male patients aged ≥65 years or adult females aged 18-64 years.

In 26 cases (35%; 23 serious cases), one or more co-suspect drugs in addition to leuprolide were reported. This set of cases included 3 cases with a fatal outcome:

- DE-ABBVIE-14P-062-1280797-00: A 78-year-old male with prostate cancer who experienced a cerebrovascular accident during treatment/overdose with leuprolide and co-suspect phenprocoumon;
- US-ABBOTT-11P-163-0723628-00: A 41-year-old female with endometriosis who died in the context of treatment/overdose with methadone and cocaine reported as co-suspect drugs; and
- CA-TOLMAR, INC.-19CA000860: A 72-year-old male with prostate cancer who died in the context of treatment/overdose with leuprolide and co-suspect morphine.

In 26 cases (34.7%; 22 serious cases), additional clinical events (signs, symptoms or diagnoses) were reported and leuprorelin was the only suspect drug. This set of cases included 3 cases with fatal outcomes:

- JP-ABBVIE-20P-087-3313439-00: An 87-year-old male with prostate cancer from whom accidental overdose was reported and who died in the context of Pneumonia, Urinary tract infection and Platelet count decreased;
- IE-SANOFI-SYNTHELABO-A01200711882: An 84-year-old male with prostate cancer from whom accidental overdose was reported and who died in the context of Chronic obstructive pulmonary disease; and
- CA-ABBOTT-10P-028-0617247-00: A 57-year-old male with prostate cancer from whom unspecified overdose was reported; additional adverse events were Feeling of despair, Depressed level of consciousness, Decreased appetite and Asthenia.

In the remaining 23 cases (30.7%; all non-serious), leuprolide was the only suspect drug and no clinical signs, symptoms or disorders were reportedly associated with the overdose.

The EVDAS received a total of 24,079 cases over an approximately 18-year period, with the earliest case received in 2003. Of these, 60 cases reported one of the Preferred terms of interest. Forty-seven of the 60 overdose cases (78%) were spontaneous reports and 12 (20%) were from studies; the source was unknown in one case. Countries reporting 3 or more overdose cases were Germany (15 cases), Canada (10 cases), United States (9 cases), Japan (7 cases), United Kingdom (5 cases), and France (4 cases). Of the 60 cases, 40 (67%) were serious, including 5 (8%) reporting a fatal outcome. The indication for use of leuprolide was reported in 41 cases and included prostate cancer (30 cases), endometriosis (6 cases), other gynecological indications (3 cases) and precocious puberty (2 cases). Consistent with the demographic profile of the approved indications, most cases describe male patients aged ≥65 years or adult females aged 18-64 years.

In 21 cases (35.0%; all serious), one or more co-suspect drugs in addition to leuprolide were reported. This set of cases included 2 cases with fatal outcomes:
− DE-MEDA-M-EU-2014100259: A case of Cerebrovascular accident in an elderly male with prostate cancer where phenprocoumon was reported as co-suspect (presumably the same case as DE-ABBVIE-14P-062-1280797-00 stored in FAERS); and
− US-ABBOTT-11P-163-0723628-00: A case of fatal overdose in a female adult with endometriosis where cocaine was reported as co-suspect (stored also in FAERS with methadone reported as a further co-suspect drug).

In 23 cases (38%; 19 serious cases), additional clinical events (signs, symptoms, or diagnoses) were reported and leuprorelin was the only suspect drug, although concomitant medications were reported in 11 of these cases. This set of cases included 3 cases with a fatal outcomes:
− JP-EMA-DD-20200804-shaik_i-105047: A >85-year-old male with prostate cancer from whom accidental overdose was reported and who died from Pneumonia with Urinary tract infection and Platelet count decreased reported as additional adverse events (presumably the same case as JP-ABBVIE-20P-087-3313439-00 stored in FAERS);
− JP-EMA-20110907-syelurip-170428655: A 65–84-year-old male with prostate cancer from whom the fatal events of Pneumothorax and Interstitial lung disease were reported in the context of unspecified overdose; and
− FR-ASTELLAS-2021US000605: A 65–84-year-old male with prostate cancer from whom unspecified overdose and death of unknown cause was reported; additional adverse events were Nausea and Decreased appetite.

In the remaining 16 cases (26.7%; all non-serious), leuprorelin was the only suspect drug and no clinical signs, symptoms or disorders were reportedly associated with the overdose (PT "No adverse event").

Overall, approximately one third of overdose cases associated with leuprolide reported in FADERS and EVDAS describe co-suspect drugs that provided a plausible alternative explanation for the reported clinical events; another third of cases do not report co-suspect drugs but the additional clinical events were heterogeneous without patterns suggestive of typical clinical manifestations of leuprorelin overdose; and in the remaining third of cases, leuprorelin overdose was not associated with any clinical signs or symptoms. In conclusion, review of the data retrieved from FAERS and EVDAS did not point to a safety concern regarding overdosage of leuprolide.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data / The Applicant's Position:

Camcevi™ 42 mg has not been approved or marketed anywhere in the world, nor has it been withdrawn from marketing / registration in any country.

Postmarketing Data of Marketed Leuprolide Products

Approved LD Labeling: During postmarketing surveillance, which included other dosage forms and other patient populations, the following AEs were reported in the approved LD labeling (AbbVie Inc, 2018):

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticarial, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (eg, joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular system – hypotension, myocardial infarction; Endocrine system – diabetes; Gastrointestinal system – hepatic dysfunction; Hemic and lymphatic system – decreased white blood cells; Integumentary system – hair growth; Central/peripheral nervous system – convulsion, spinal fracture/paralysis, hearing disorder; Miscellaneous – hard nodule in throat, weight gain, increased uric acid; Musculoskeletal system – tenosynovitis-like symptoms; Respiratory System – respiratory disorders;

Changes in bone density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

FAERS Database: The FDA's FAERS database contains AEs submitted to the FDA each quarter. The up-to-date database for Q1 of 2017 through Q4 of 2017 (current) was searched for AEs with "leuprolide or Lupron or Eligard" being the keyword for "DRUGNAME" and "ps" (primary suspect) being the keyword for "ROLE_COD". The results were filtered for "45 mg" for "DOSE_AMT" and "M or blank" for "SEX". The search results reflect any duration of treatment with leuprolide acetate. Because the FAERS database contains voluntary reports from populations of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. According to the CAVEATS section in the FAERS Database README file, "For any given report, there is no certainty that a suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions; however, the event may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or simply occurred by chance at that time."

A pivot table was constructed to identify the most frequently reported AEs (Applicant - Table 9).

For a full list of all reported AEs per subject refer to NDA Module 2.7.4., Section 2.7.4.9., Table 15 and frequency refer to NDA Module 2.7.4., Section 2.7.4.9., Table 16. Death was listed as the most commonly reported AE (190 events), although analysis of outcome codes demonstrated that this number was underestimated. The results identified 302 deaths that were primarily linked to the use of leuprolide acetate; this amounted to 23.54% of subjects reporting AEs. As prostate cancer is a serious disease, with approximately 26,000 projected deaths due to prostate cancer in 2017 (Siegel et al., 2017), it is not surprising that death comprised a large portion of the AEs. In addition, this disease comprises an aging population; all deaths in this search that reported an age occurred in subjects at least 60 years old.

Many of the other reported AEs were related to improper product use: syringe issue (7.01%), wrong technique in product usage process (4.36%), intercepted medication error (2.57%),

product reconstitution quality issue (1.87%), and drug dose omission (1.40%). Detailed instructions will be included with the Sponsor's product to decrease the likelihood of product administration errors. Other frequently reported AEs included prostate cancer (4.21%), prostatic specific antigen increased (2.96%), hot flush (1.56%), and cardiac failure (1.40%). It is also noted that most of the reported AEs in FAERS have been recognized in the published literature and approved LD labeling.

Applicant - Table 17 Ten Most Frequent Adverse Events Related to Leuprolide Acetate in the FAERS Database (2017Q1 to 2017 Q4)

Preferred term	Number of Events Reported	Frequency of Event[a] (%)
Death	190	14.81%
Syringe issue	90	7.01%
Wrong technique in product usage process	56	4.36%
Prostate cancer	54	4.21%
Prostatic specific antigen increased	38	2.96%
Intercepted medication error	33	2.57%
Product reconstitution quality issue	24	1.87%
Hot flush	20	1.56%
Cardiac failure	18	1.40%
Drug dose omission	18	1.40%

[a]Based on total number of events reported in the FAERS Database

The FDA's Assessment:

(b) (4)

On April 1, 2021, this clinical reviewer queried the FAERS database for cumulative reports of all adverse events associated with leuprolide. The statistical algorithm that FDA uses to datamine FAERS reports, the multi-item gamma poissonshrinker (MGPS), produces empirical Bayesian geometric mean (EGBM) scores, the lower and upper 90% confidence limits of which are denoted EB_{05} and EB_{95}, respectively. Associations with EB_{05} values ≥ 2 are conventionally considered noteworthy safety signals. This query retrieved two Preferred terms – Hot flush and Vasodilation – with EB_{05} values above 2 (32.0 and 7.2, respectively). Hot flush and vasodilation

are known pharmacodynamic effects of androgen deprivation and are adequately described in Section 6 of the proposed Prescribing Information.

Expectations on Safety in the Postmarket Setting

Data / The Applicant's Position:

Based on the safety experience gained with Camcevi™ 42 mg in the 12-month Phase 3 Study FP01C-13-001 and its 12-month safety extension Study FP01C-13-001-EX, it is anticipated that the post-marketing safey profile resembles that of approved and marketed leuprolide depot forms. As Camcevi™ 42 mg represents a ready-to-use drug product, medication errors are likely to be of less significance as compared to marketed leuprolide depot formulations.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.11 Integrated Assessment of Safety

Data / The Applicant's Position:

Across Sponsor-conducted studies, no new AEs were identified for Camcevi™ 42 mg compared to previously-approved leuprolide products. The most common AEs were hot flush, hypertension, pain in extremity, fatigue, injection pain, arthralgia, nocturia, back pain, and nasopharyngitis; these are in line with safety issues identified in the approved labeling for Lupron® and AEs reported in the published literature. ECG recordings identified clinically significant QT prolongation in 5 subjects due to leuprolide treatment. However, this is a known risk for currently marketed leuprolide products (AbbVie Inc, 2018).

Three deaths occurred in the Sponsor studies, attributed to cerebrovascular accident, pulmonary embolism, and metastatic prostate cancer to lungs and acute kidney injury; all fatal events were determined to be unrelated to the investigational product. No deaths were reported in the approved Lupron® labeling, although the labels warns of an increased risk of developing myocardial infarction, sudden cardiac death, and stroke in association with the use of GnRH agonists in men (AbbVie Inc, 2018).

A search of the FAERS database during the period of 2017 Q1 to 2017 Q4 identified 302 deaths that were primarily linked to the use of leuprolide acetate. However, as prostate cancer is a serious disease, with approximately 26,000 projected deaths due to prostate cancer in 2017 (Siegel et al., 2017), it is not surprising that death comprised a large portion of the AEs (23.54%). In addition, this disease comprises an aging population; all deaths in this search that reported an age occurred in subjects at least 60 years old.

Camcevi™ 42 mg proved to be safe and well tolerated in the clinical studies, raising no specific safety or tolerability concern. Although the overall exposure to Camcevi™ 42 mg is comparably

low, the PK/PD cross-study comparison exercises are deemed appropriate for bridging to the leuprorelin acetate safety database.

The nature of the AEs reported in the Sponsor's studies were consistent with those reported for the LD, Lupron®, and in the published literature for subjects treated with 6-month leuprolide depot formulations. Overall, the Sponsor has demonstrated that Camcevi™ 42 mg is generally well-tolerated and effective in suppressing testosterone levels for the treatment of prostate cancer (refer to NDA Module 2.5, Section 2.5.6.4).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Known adverse effects of androgen deprivation include acceleration of atherosclerosis, prolongation of the QT interval, osteoporosis, hyperglycemia, anemia, cognitive decline, gynecomastia, hot flashes, and loss of libido. Many of these effects are nonspecific and common in aging individuals. The overall pattern of AEs reported in FP01C-13-001 and FP01C-13-001-EX is consistent with that expected in men in the demographic group and the disease under study, and are consistent with toxicities reported in published clinical trials and post-marketing reports of leuprolide.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:
FDA's efficacy evaluation was based on data from FP01C-13-001. Study FP01C-13-001 met its primary objective of achieving and maintaining serum testosterone suppression to ≤ 50 ng/dL from Day 28 through Day 336 by demonstrating that the lower bound of the 95% CI around the suppression rate at Day 336 was greater than 90%. The results were supported by sensitivity analyses and secondary endpoints. There are no major statistical issues.

8.4 Conclusions and Recommendations

The FDA's Assessment:
The clinical review team recommends regular approval of leuprolide injectable emulsion as treatment for adult patients with advanced prostate cancer. This recommendation is based on an acceptable rate of achieving and maintaining serum testosterone suppression to ≤ 50 ng/dL from Day 28 through Day 336. The safety profile of leuprolide injectable emulsion was found to comparable to that of leuprolide acetate and within the expected range for the patient population being studied.

Because Camcevi is a mesylate salt and all other marketed leuprolide products are acetate salts, and because both mesylate and acetate leuprolide products may be used as ADT in patients with prostate cancer, it is important that the drug strength be expressed in a manner that minimizes the potential for medication errors. In marketed leuprolide acetate products, 45 mg contains 42 mg of the free base form of leuprolide, whereas with leuprolide mesylate, 48 mg contains 42 mg of the free base form of leuprolide. Current USP nomenclature policy directs that strength of drugs be named according to their freebase forms rather than salt forms. The Camcevi Prescribing Information will therefore present the recommended dosage of leuprolide injectable emulsion as 42 mg subcutaneously every 6 months. See Section 6.2 of this review for additional details.

X X

Primary Statistical Reviewer Statistical Team Leader

X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer this efficacy supplement to an advisory committee because the application did not raise significant public health questions regarding the role of leuprolide injectable emulsion for the proposed indication. The demonstrated benefit-risk profile for leuprolide injectable emulsion is favorable in adult patients advanced prostate cancer.

10 Pediatrics

The Applicant's Position

Foresee submitted an Initial Pediatric Study Plan (iPSP), 25 May 2017, under IND 103206. Acknowledgement of the plan that FDA waive the requirement for pediatric assessments for LMIS 50 mg was received on 15 August 2017. Subsequently, Foresee submitted an Agreed iPSP, dated 24 August 2017 (IND 103206). FDA agreement on the Agreed iPSP was received on 20 September 2017.

The FDA's Assessment:

Prostate cancer rarely occurs in children, and the FDA granted a pediatric waiver for leuprolide injectable emulsion.

11 Labeling Recommendations

Below table provides the only revision to the labeling at this time:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
		(b) (4)

The Applicant's Position:
This is a minor revision to align FULL PRESCRIBING INFORMATION: CONTENTS to subheading section 5.5 WARNINGS AND PRECAUTIONS. The is no impact to the labeling information.

The FDA's Assessment:
FDA did not agree to changing the subheading of Section 5.5 as described above, and instead the subheading is called QT/Qtc Prolongation.

Generally, safety and efficacy data from FP01C-13-001 were included in Sections 6 and 14, respectively.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team does not recommend a risk evaluation and mitigation strategy to ensure safe and effective use of leuprolide injectable emulsion for the indicated population given the well-established safety profile of leuprolide products.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
There will be one postmarketing commitment for this application, as follows:

PMC 3614-1
Develop a separate, specific, complimentary method to determine the degradant at RRT (b) (4) *. Submit a CBE-30 supplement to update the drug product specifications with the new method for RRT* (b) (4) *. In the supplement, provide a description of the new method as well as the validation data.*

Final Report Submission
06/2022

14 Division Director (DHOT) (NME ONLY)

X _____

15 Division Director (OCP)

X

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X _____

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1 References

The Applicant's References:

AbbVie Inc (2018). Lupron Injection (leuprolide acetate) Prescribing Information (NDA 019010) (North Chicago, IL: AbbVie Inc).

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The FDA's References:
None

19.2 Financial Disclosure

The Applicant's Position:
Refer to Sources of Clinical Data, Study Result, Financial Disclosure summarized above.

The FDA's Assessment:

Covered Clinical Study (Name and/or Number):* FP01C-13-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3 Nonclinical Pharmacology/Toxicology

The FDA's Assessment:
See Section 5.5

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1 Summary of Bioanalytical Method Validation and Performance

Concentrations of leuprolide, testosterone, and leuteinizing hormone (LH) in human serum in Study FP01C-13-001 were measured using bioanalytical methods based on liquid chromatography tandem mass spectrometry (LC-MS/MS) for leuprolide and testosterone and Ultra-Sensitive lumELISA for LH. All bioanalytical method were validated with respect to linearity, sensitivity, accuracy, precision, dilution, selectivity, hemolyzed serum, lipemic serum, batch size, recovery, matrix effect, and carryover, by (b) (4), the site of which has been inspected in (b) (4) by OSIS. See tables below for the bioanalytical method validation summary for each of the analytes.

Table 18. Summary of bioanalytical method validation for leuprolide in Study FP01C-13-001.

Report Title	Validation of a Method for the Determination of Leuprolide in Human Serum by LC-MS/MS
Study Number	(b) (4)398-1301
Analyte Name	Leuprolide
Internal Standard (IS)	Leuprolide-d_5
Analytical Method Type	LC-MS/MS
Extraction Method	Solid phase
Sample Volume	200 µL
QC Concentrations	0.1, 0.3, 4, 90, and 160 ng/mL
Standard Curve Concentrations	0.1, 0.2, 2, 6, 20, 60, 180, and 200 ng/mL
Lower Limit Of Quantitation	0.1 ng/mL
Upper Limit Of Quantitation	200 ng/mL
Average Recovery of Analyte (%)	100.6%
Average Recovery of Internal Standard (%)	NA[a]
LLOQ QC Intraday Precision Range (%CV)	4.2 to 7.3
LLOQ QC Intraday Accuracy Range (%RE)	-6.9 to 13.0
Analytical QC Intraday Precision Range (%CV)	0.6 to 3.5
Analytical QC Intraday Accuracy Range (%RE)	0.6 to 13.0
LLOQ QC Interday Precision (%CV)	9.5
LLOQ QC Interday Accuracy (%RE)	2.0
Analytical QC Interday Precision Range (%CV)	1.0 to 3.6
Analytical QC Interday Accuracy Range (%RE)	0.6 to 9.7
Stock Solution Stability in Methanol	322 Days at -20°C 7 Hours at Ambient Temperature
Processed Sample Stability	149 Hours at 4°C
Benchtop Stability in Human Serum	17.5 Hours at Ambient Temperature
Freeze/Thaw Stability in Human Serum	5 Cycles at -20°C and -70°C
Long-term Storage Stability in Human Serum	982 Days at -20°C and -70°C
Dilution Integrity	400 ng/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS
Hemolyzed Serum Test	No impact on assay performance
Lipemic Serum Test	No impact on assay performance

[a] Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

Source: EDR 5.3.1.4 leuprolide sample analytical report.

Table 19. Summary of bioanalytical method validation for testosteron in Study FP01C-13-001.

Report Title	Validation of a Method for the Determination of Testosterone in Human Serum by LC-MS/MS
Study Number	(b) (4) 398-1302
Analyte Name	Testosterone
Internal Standard (IS)	Testosterone-d_5
Analytical Method Type	LC-MS/MS
Extraction Method	Liquid-liquid
Sample Volume	100 µL
QC Concentrations	0.05, 0.15, 2.5, and 8 ng/mL
Standard Curve Concentrations	0.05, 0.1, 0.3, 1, 2, 5, 9, and 10 ng/mL
Lower Limit Of Quantitation	0.05 ng/mL
Upper Limit Of Quantitation	10 ng/mL
Average Recovery of Analyte (%)	71.8
Average Recovery of Internal Standard (%)	NA[a]
LLOQ QC Intraday Precision Range (%CV)	6.3 to 9.3
LLOQ QC Intraday Accuracy Range (%RE)	-15.2 to -1.0
Analytical QC Intraday Precision Range (%CV)	1.1 to 3.2
Analytical QC Intraday Accuracy Range (%RE)	-3.3 to 1.3
LLOQ QC Interday Precision (%CV)	10.1
LLOQ QC Interday Accuracy (%RE)	-9.6
Analytical QC Interday Precision Range (%CV)	1.5 to 3.4
Analytical QC Interday Accuracy Range (%RE)	-2.0 to 0.6
Stock Solution Stability in Acetonitrile	4 Years at -10°C to -25°C[b] 17 Hours at Ambient Temperature
Processed Sample Stability	143 Hours at 4°C
Benchtop Stability in Serum	16.5 Hours at Ambient Temperature
Freeze/Thaw Stability in Serum	5 Cycles at -20°C and -70°C
Long-term Storage Stability in Serum	940 Days at -20°C and -70°C
Dilution Integrity	20 ng/mL diluted 20-fold
Interference Test for Leuprolide	No interference from co-administered drug Leuprolide to Testosterone
Interference Test for eight potential co-administered over-the-counter (OTC) drugs (ranitidine, acetylsalicylic acid, naproxen, acetaminophen, nicotine, ibuprofen, ketoprofen, and methotrexate)	No interference from co-administered OTC drugs to testosterone
2% Hemolyzed Plasma Test	No impact on assay performance
Matrix Equivalence Test	No difference between male and female human serum

[a] Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.
[b] Refer to Certificate of Analysis in Section 20

Source: EDR 5.3.1.4 testosterone sample analytical report.

Table 20. Summary of bioanalytical method validation for luteinizing hormone (LH) in Study FP01C-13-001.

Report Title	Determination of Luteinizing Hormone in Human Serum by Ultra-Sensitive lumELISA
Report Number	(b) (4)42-1504
Analyte Name and synonym	Luteinizing Hormone, LH
Sample Volume:	70 µL
Analytical Method Type	Chemiluminescense ELISA
Sample Processing Method	None
Calibration Range:	0.05 – 25.0 IU/L
LLOQ QC (Kit-provided Standard 2)	0.05 IU/L
BLLOQ QC (Kit-provided Standard 3 diluted 2x in Standard 1)	1.00 IU/L
ULOQ QC (Kit-provided Standard 7 Diluted 2x in Standard 1)	25.0 IU/L
Endogenous Matrix QC Concentrations (Nominal determined from mean of precision and accuracy runs)	KER150316-02: 1.68 IU/L KER150316-03: 5.95 IU/L KER150316-04: 15.9 IU/L
QC Intra-batch Precision (%CV)	0.9% to 12.8%
QC Intra-batch Accuracy (%RE)	-6.0% to 23.0%
QC Inter-batch Precision (%CV)	4.1% to 14.4%
QC Inter-batch Accuracy (%RE)	-8.2 % to 10.0%
Benchtop Stability in Human Serum	40 Hours at Room Temperature
Freeze/thaw Stability in Human Serum	5 Cycles at -70°C and -20°C, thawed at room temperature
Long-term Storage Stability in Human Serum	122 Days at -70°C; At least 868 days stability at -20 °C.
Dilution Linearity	25 IU/L diluted 1X, 2X, 4X, 8X, and 10X
Normal Range- 30 Male Human Serum lots	1.25 to 19.8 IU/L
Selectivity (10 lots, spiked 5IU/L)	>80% lots tested within 100±25% Recovery

Source: EDR 5.3.1.4 LH sample analytical report.

19.4.2 Clinical Pharmacokinetics and Pharmacodynamics Assessments

Clinical PK

The clinical PK of leuprolide was evaluated in Study FP01C-13-001 in 33 patients in Part I and another 99 patients in Part II of the study. Table 19 and Table 20 represent leuprolide PK

parameters following the first and second doses.

Table 21. Summary of arithmetic mean (SD) serum PK parameters of leuprolide after LMIS 50 mg SC injections at Part I of Study FP01C-13-001.

Part I						
	First Dose			Second Dose		
PK Parameter	N	Mean	SD	N	Mean	SD
C_{max}, ng/mL	31	94.5	53.7	29	99.0	73.0
T_{max}, h	31	3.23 (1.17, 7.90)		29	2.08 (1.17, 8.00)	
C_{wk4}, ng/mL	31	1.04	0.863	29	1.64	0.983
C_{mon6}, ng/mL	29[a]	0.497	0.610	29	0.511	0.488
$AUC_{0\text{-}4wks}$, day·ng/mL	31	91.6	47.9	29	125	57.3
$AUC_{0\text{-}6mon}$, day·ng/mL	29[a]	224	87.3	29	268	88.1
$C_{avg(0\text{-}6mon)}$, ng/mL	29[a]	1.34	0.519	29	1.59	0.525

T_{max}: Median (Min, Max); a: two subjects' PK parameters were not reportable. N:Number of subjects

Source: EDR Study FP01C-13-001 CSR.

Table 22. Summary of arithmetic mean (SD) serum PK parameters of leuprolide after LMIS 50 mg SC injections at Part II of Study FP01C-13-001.

Part II						
	First Dose			Second Dose		
PK Parameter	N	Mean	SD	N	Mean	SD
C_{max}, ng/mL	94	99.7	65.6	97	93.7	60.8
T_{max}, h[a]	94	3.67 (2.83, 24.00)		97	3.78 (2.87, 5.17)	
C_{wk4}, ng/mL	94	1.47	2.57	96[b]	2.40	4.05
C_{mon6}, ng/mL	92[a]	0.370	0.313	94[b]	0.410	0.538
$AUC_{0\text{-}4wks}$, day·ng/mL	94	103	62.4	96[b]	131	91.4
$AUC_{0\text{-}6mon}$, day·ng/mL	92[a]	219	108	94[c]	250	160
$C_{avg(0\text{-}6mon)}$, ng/mL	92[a]	1.31	0.643	94[c]	1.49	0.950

T_{max}: Median (Min, Max); [a]: not reportable for 2 subjects; [b]: not reportable for 1 subject; [c]: not reportable for 3 subjects.

Source: EDR Study FP01C-13-001 CSR.

Assessment of Covariate

The Applicant combined the PK data from Part I and Part II of Study FP01C-13-001 and conducted a noncompartmental analysis (NCA) to compare the overall PK of leuprolide following single dose (Period 1) and multiple dose (i.e., second dose, Period 2). It is noted that compared to the single SC dose, a seond SC dose will reach similar C_{max} and increase $AUC_{0\text{-}6mon}$ by 17% with regard to geometric mean values.

Table 23. Summary of geometric mean (CV%) of serum PK parameters of leuprolide by period and overall.

	Period 1 (n=125)	Period 2 (n=126)	Overall (n=251)
C_{max} (ng/mL)			
Geo. Mean (Geo. CV%)	79.6 (78.2)	78.7 (67.4)	79.1 (72.6)
Median [Min, Max]	85.7 [7.66, 343]	78.9 [16.3, 356]	80.0 [7.66, 356]
T_{max} (h)			
Geo. Mean (Geo. CV%)	3.44 (36.2)	3.41 (30.3)	3.42 (33.3)
Median [Min, Max]	3.67 [1.17, 24.0]	3.67 [1.17, 8.00]	3.67 [1.17, 24.0]
$C_{avg(0\text{-}6mon)}$ (ng/mL)			
Geo. Mean (Geo. CV%)	1.17 (54.5)	1.37 (45.3)	1.27 (50.6)
Median [Min, Max]	1.12 [0.140, 3.33]	1.39 [0.327, 8.46]	1.24 [0.140, 8.46]
Missing	4 (3.2%)	3 (2.4%)	7 (2.8%)
$AUC_{0\text{-}4wks}$ (ng·day/mL)			
Geo. Mean (Geo. CV%)	84.5 (65.3)	110 (61.1)	96.4 (65.0)
Median [Min, Max]	91.2 [17.4, 371]	110 [23.2, 494]	99.8 [17.4, 494]
Missing	0 (0.0%)	1 (0.8%)	1 (0.4%)
$AUC_{0\text{-}6mon}$ (ng·day/mL)			
Geo. Mean (Geo. CV%)	197 (54.5)	230 (45.3)	213 (50.6)
Median [Min, Max]	188 [23.5, 560]	234 [54.9, 1420]	209 [23.5, 1420]
Missing	4 (3.2%)	3 (2.4%)	7 (2.8%)
C_{mon6} (ng/mL)			
Geo. Mean (Geo. CV%)	0.346 (71.0)	0.364 (77.1)	0.355 (73.9)
Median [Min, Max]	0.345 [0.102, 3.35]	0.344 [0.102, 4.45]	0.345 [0.102, 4.45]
Missing	14 (11.2%)	15 (11.9%)	29 (11.6%)
C_{wk4} (ng/mL)			
Geo. Mean (Geo. CV%)	NA (NA)	NA (NA)	NA (NA)
Median [Min, Max]	0.795 [0.00, 18.1]	1.44 [0.00, 30.3]	1.09 [0.00, 30.3]
Missing	0 (0.0%)	1 (0.8%)	1 (0.4%)

Source: EDR 5.2 PK report FSEE-CSC-101.

A post-hoc analysis using ANCOVA was applied to assess the impact of race, body weight, and age on on serum leuprolide PK and serum testosterone PD.

Table 24. Summary demographics of the PK population in Study FP01C-13-001.

Demographic		Overall (n = 131)
Race	White	118 (90.1%)
	Black or African American	8 (6.1%)
	Asian	4 (3.1%)
	Other	1 (0.8%)
Age (years)	Mean (CV%)	70.9 (12.1)
	Median [Min, Max]	71.0 [51.0, 88.0]
Weight (kg)	Mean (CV%)	85.5 (18.2)
	Median [Min, Max]	84.3 [54.0, 134]

Source: Study FSEE-CSC-101 Table 5.1.1

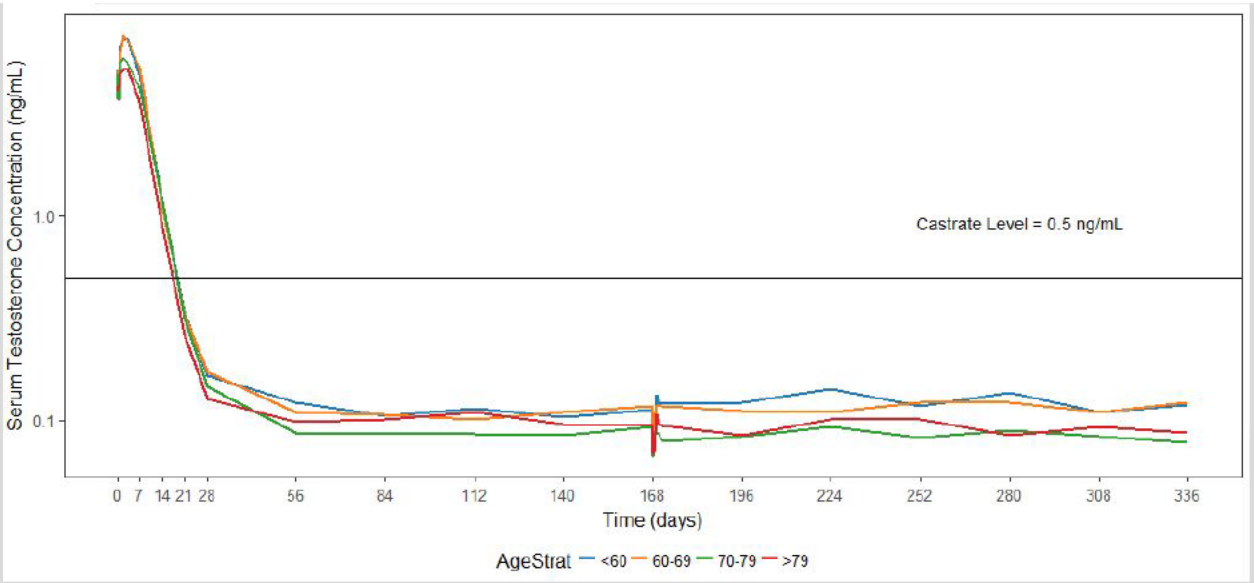
Results showed that the race does not have statistically significant impact on the leuprolide PK or testosterone PD. The serum concentration of leuprolide will increase with increased age and decreased body weight, however does not have impact on the serum concentration of testosterone. The impact of race, age, and body weight was therefore deemed clinically irrelevant.

Table 25. Summary of geometric mean (CV%) of serum PK parameters of leuprolide stratified by age.

	Age Groups (years)			
	< 60 (n = 25)	60–69 (n = 82)	70–79 (n = 101)	> 79 (n = 43)
Cmax (ng/mL)				
Geo. Mean (Geo. CV%)	55.0 (62.8)	74.6 (74.0)	81.9 (72.3)	101 (63.6)
Median [Min, Max]	56.5 [20.4, 191]	79.0 [7.66, 299]	80.6 [19.1, 356]	100 [20.2, 343]
Tmax (h)				
Geo. Mean (Geo. CV%)	3.24 (36.2)	3.61 (33.5)	3.28 (33.0)	3.53 (30.9)
Median [Min, Max]	3.67 [1.22, 4.17]	3.67 [1.50, 24.0]	3.67 [1.17, 5.17]	3.73 [1.60, 8.00]
Cavg(0-6mon) (ng/mL)				
Geo. Mean (Geo. CV%)	0.858 (37.2)	1.13 (55.4)	1.33 (46.0)	1.71 (33.0)
Median [Min, Max]	0.871 [0.327, 1.73]	1.04 [0.140, 8.46]	1.38 [0.187, 3.33]	1.74 [0.937, 3.59]
Missing	1 (4.0%)	4 (4.9%)	1 (1.0%)	1 (2.3%)
AUC0-4wks (ng·day/mL)				
Geo. Mean (Geo. CV%)	65.4 (57.5)	86.2 (64.5)	99.8 (62.2)	138 (51.9)
Median [Min, Max]	72.4 [23.2, 202]	87.1 [17.4, 454]	110 [25.2, 437]	132 [39.7, 494]
Missing	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
AUC0-6mon (ng·day/mL)				
Geo. Mean (Geo. CV%)	144 (37.2)	190 (55.4)	224 (46.0)	287 (33.0)
Median [Min, Max]	146 [54.9, 290]	175 [23.5, 1420]	231 [31.5, 560]	292 [157, 603]
Missing	1 (4.0%)	4 (4.9%)	1 (1.0%)	1 (2.3%)
Cmon6 (ng/mL)				
Geo. Mean (Geo. CV%)	0.261 (52.4)	0.293 (51.9)	0.374 (82.0)	0.490 (77.8)
Median [Min, Max]	0.247 [0.109, 0.711]	0.291 [0.123, 0.783]	0.381 [0.102, 4.45]	0.478 [0.138, 3.35]
Missing	7 (28.0%)	15 (18.3%)	5 (5.0%)	2 (4.7%)
Cwk4 (ng/mL)				
Geo. Mean (Geo. CV%)	0.766 (90.7)	NA (NA)	NA (NA)	1.65 (92.8)
Median [Min, Max]	0.783 [0.119, 3.18]	0.913 [0.00, 30.3]	1.06 [0.00, 13.2]	1.57 [0.361, 24.7]
Missing	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)

Source: FSEE-CSC-101 Table 5.4.10

Figure 10. Serum testosterone time-concentration profile stratified by age.



Source: FSEE-CSC-101 Figure 5.5.6.

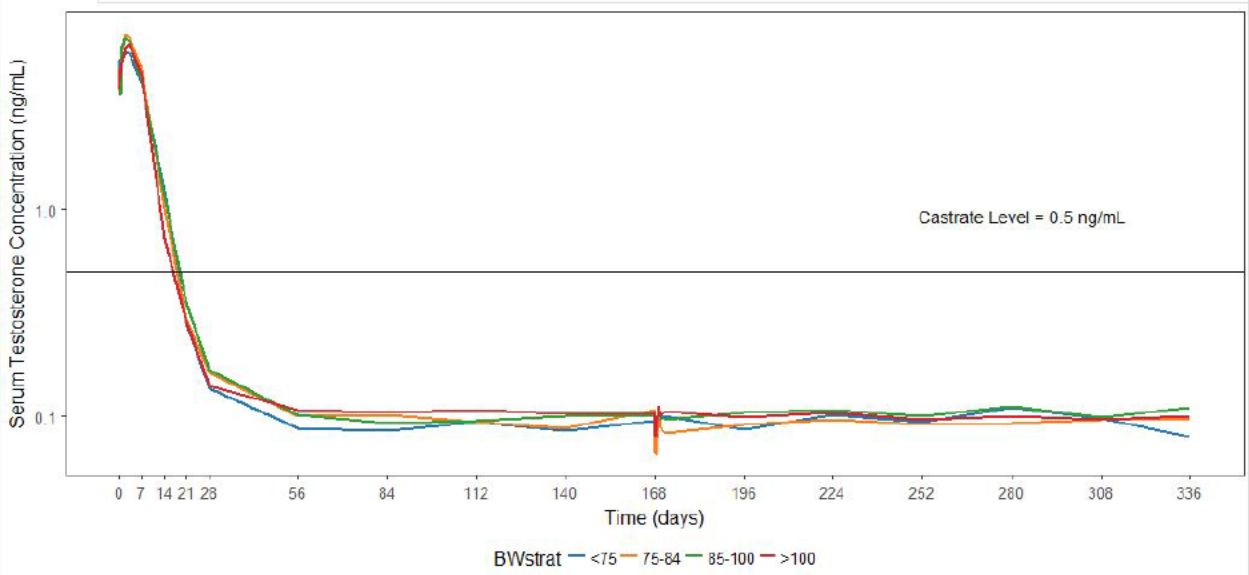
Table 26. Summary of geometric mean (CV%) of serum PK parameters of leuprolide stratified by body weight.

	Body Weight Categories			
	< 75 kg (n = 59)	75–84 kg (n = 72)	85–100 kg (n = 87)	> 100 kg (n = 33)
Cmax (ng/mL)				
Geo. Mean (Geo. CV%)	102 (68.2)	77.0 (75.7)	74.6 (60.2)	61.9 (89.3)
Median [Min, Max]	112 [19.1, 343]	77.4 [20.2, 299]	73.2 [21.0, 236]	66.1 [7.66, 356]
Tmax (h)				
Geo. Mean (Geo. CV%)	3.20 (33.8)	3.28 (34.2)	3.61 (22.3)	3.69 (49.9)
Median [Min, Max]	3.50 [1.17, 4.67]	3.57 [1.17, 7.52]	3.72 [1.50, 8.00]	3.83 [1.22, 24.0]
Cavg(0-6mon) (ng/mL)				
Geo. Mean (Geo. CV%)	1.50 (49.7)	1.21 (47.1)	1.21 (51.6)	1.18 (51.9)
Median [Min, Max]	1.52 [0.297, 3.59]	1.22 [0.187, 3.13]	1.22 [0.140, 3.22]	1.08 [0.669, 8.46]
Missing	3 (5.1%)	1 (1.4%)	2 (2.3%)	1 (3.0%)
AUC0-4wks (ng·day/mL)				
Geo. Mean (Geo. CV%)	130 (65.2)	91.2 (57.8)	90.5 (58.1)	75.5 (74.8)

Median [Min, Max]	128 [26.9, 494]	90.1 [27.4, 283]	97.6 [18.5, 259]	91.2 [17.4, 454]
Missing	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
AUC0-6mon (ng·day/mL)				
Geo. Mean (Geo. CV%)	252 (49.7)	204 (47.1)	203 (51.6)	198 (51.9)
Median [Min, Max]	255 [49.9, 603]	206 [31.5, 525]	205 [23.5, 541]	182 [112, 1420]
Missing	3 (5.1%)	1 (1.4%)	2 (2.3%)	1 (3.0%)
Cmon6 (ng/mL)				
Geo. Mean (Geo. CV%)	0.365 (74.9)	0.374 (68.9)	0.368 (83.1)	0.268 (52.1)
Median [Min, Max]	0.351 [0.103, 3.35]	0.359 [0.109, 2.69]	0.348 [0.102, 4.45]	0.257 [0.111, 0.636]
Missing	4 (6.8%)	8 (11.1%)	12 (13.8%)	5 (15.2%)
Cwk4 (ng/mL)				
Geo. Mean (Geo. CV%)	1.30 (130)	1.08 (99.8)	NA (NA)	NA (NA)
Median [Min, Max]	1.14 [0.124, 24.7]	1.09 [0.257, 18.1]	1.12 [0.00, 13.2]	0.824 [0.00, 30.3]
Missing	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)

Source: FSEE-CSC-101 Table 5.4.12

Figure 11. Serum testosterone time-concentration profile stratified by body weight.



Source: FSEE-CSC-101 Figure 5.5.7.

Signatures

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	Signature: Lili Pan -S Digitally signed by Lili Pan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lili Pan -S, 0.9.2342.19200300.100.1.1=2001832999 Date: 2021.05.18 15:50:16 -04'00'			
Clinical Pharmacology (TL)	Salaheldin Hamed, PhD	OCP/DCPII	Sections: 6, 19.4	Select one: ___ Authored x Approved
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Pharm/Tox	Haw-Jyh Chiu, PhD	OOD/DHOT	Sections: 5	Select one: x Authored x Approved
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Pharm/Tox (TL)	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	Select one: x Authored x Approved
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Biometrics Reviewer	Lijun Zhang, PhD	OB/DBV	Sections: 8	Select one: X Authored ___ Approved
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Biometrics (TL)	Mallorie Fiero, PhD	OB/DBV	Sections: 8	Select one: X Authored X Approved
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Clinical Reviewer	Michael Brave, MD	OOD/DO1	Sections: 1-3, 7-15	Select one: x Authored ___ Approved
	Signature: Michael H. Brave -S Digitally signed by Michael H. Brave -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300221205, cn=Michael H. Brave -S Date: 2021.05.18 16:57:43 -04'00'			
Clinical Reviewer (TL)	Chana Weinstock, MD	OOD/DO1	Section: 1	Select one: x Authored x Approved
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Associate Director for Labeling	William Pierce, PharmD	OOD	Sections: Section 11, Prescribing Information	Select one: x Authored x Approved
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Cross-Disciplinary Team Leader (CDTL)	Chana Weinstock, MD	OOD/DO1	Sections: 1	Select one: x Authored x Approved
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Division Director (OCP)	Nam Atiqur Rahman, PhD	OCP/DCPII	Sections: 6, 19.4	Select one: ___ Authored x Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.05.18 18:58:39 -04'00'			
Division Director OB (Acting)	Shenghui Tang, PhD	OB/DBV	Sections: 6, 19.4	Select one: ___ Authored x Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.05.18 17:19 50 -04'00'			
Deputy Director	Amna Ibrahim, MD	OOD/DO1	Sections: All	Select one: ___ Authored x Approved

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